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VON WILLEBRAND'S DISEASE
IN SWEDEN

BY JÖRGEN SILVER

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VON WILLEBRAND'S DISEASE IN SWEDEN

av
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med.lic., Kr

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VON WILLEBRAND'S DISEASE IN SWEDEN

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HISTORICAL

von Willebrand's publications

It was in 1926 that von Willebrand published his first description of a familial haemorrhagic diathesis, occurring in both sexes and characterised by a prolonged bleeding time despite normal platelet count. He called the disease hereditary pseudohaemophilia.

His report included a survey of 19 previously published cases with a similar clinical picture. The earliest case that he could trace was one presented by Kehrer as early as 1876.

von Willebrand's first case was seen in a girl, Hjördis S. When first examined she was 5 years old. She belonged to a sibship of 10 children, some of whom had had more or less pronounced bleeding symptoms. Three of the sisters had died at 2–4 years of age from bleeding. Both parents had, when young, had troublesome nose-bleedings.

On further investigation von Willebrand discovered several relatives of Hjördis S. with symptoms of the same haemorrhagic diathesis, and as early as 1926 he published data about 23 bleeders. The family, now the well known Åland family, has since been studied more extensively (Eriksson et al. 1961) and is still the one with by far the largest number of members with known von Willebrand's disease.

In his publication von Willebrand gave a very good description of the clinical picture of the disease. The dominating symptoms consist of nose-bleeding, gingival bleeding, uterine bleeding and cutaneous bleeding in the form of ecchymoses and haematomas. Gastro-intestinal haemorrhage is relatively uncommon, but when it occurs, it is often serious. von Willebrand also pointed out that, in contrast with what is seen in haemophilia, joint bleeding in the Åland family was rare.

von Willebrand also carried out laboratory studies, which must be regarded as extensive for that time.

The bleeding time, as determined by the method of Duke, was prolonged to more than two hours in the severest cases, including the first one in Hjördis S. In several of the other affected relatives the bleeding time was normal.

The coagulation time was invariably normal. Clot retraction was studied only in Hjördis S. and was found to be normal. The Rumpel-Leede phenomenon showed

capillary resistance to be impaired in patients affected.

In investigation of the heredity of the bleeding tendency von Willebrand consulted a geneticist, Federley, in Helsingfors. They arrived at the conclusion that the condition was transmitted by a dominant sex-linked gene, linked to the X-chromosome. This conclusion was supported by the fact that von Willebrand had found bleeding symptoms more often in females and that all of the severe cases were seen in females, especially those with a fatal issue. These patients with severe haemorrhagic diathesis were thought to be homozygous in respect of the bleeding tendency.

von Willebrand compared the condition with other more well-known bleeding diseases, especially classical haemophilia, which, however, occurs only in males. It differs furthermore from the bleeding disease in Åland by a prolonged coagulation time and a normal capillary resistance.

Finally, von Willebrand (1926) discussed the pathogenesis of the condition and found that the bleedings could best be explained by the joint effect of a functional disorder of the platelets and a systemic lesion of the vessel walls.

The first publication on the bleeding disease, which now carries his name, was written in Swedish. In 1931 he published a second article of the subject, which was written in German and was thereby accessible to a larger number of readers.

In order to form a conception of the possibly disturbed vascular function, von Willebrand (1931) had Hjördis S. examined with capillary microscopy. The investigation showed considerable fluctuation in the blood flow through the capillaries, which were tortuous with variation in the caliber and contraction of the loops, von Willebrand, however, pointed out that tortuous capillaries occur also in other diseases, e.g. such vascular affections as arteriosclerosis and nephritis.

In that article he also published a small section on therapy. He felt that blood transfusions were useful not only for replacing blood loss, but also for controlling bleeding.

In the beginning of the 1930s von Willebrand contacted the German researcher, R. Jürgens, who had together with Morawitz (1930) described a so-called capillary thrombometer for measuring the "thrombo-

sis time". With this apparatus blood is pressed to and fro through a glass capillary tube. This results in the formation of a plug, which normally occludes the capillary after about 4 minutes. The so-called thrombosis-time was, according to Morawitz and Jürgens, well correlated with the bleeding time but not with the coagulation time. On microscopic examination the plug was found to consist mainly of platelets.

von Willebrand and Jürgens together studied members of the Åland family with the use of the capillary thrombometer. (von Willebrand & Jürgens 1933:a). The thrombosis time for Hjördis S. and some of her relatives was found to be extremely prolonged, up to 30–40 minutes, while in the other bleeders examined the time was prolonged by only a few minutes or was even normal.

As to the heredity of the disease, von Willebrand 1933 revised his previous opinion and now thought it to be due to an autosomal dominant gene. He thus no longer believed in a sex-linked dominant heredity with the gene linked to the X-chromosome, partly because he had seen cases where the bleeding tendency had evidently been inherited from father to son, while the mother had apparently not been affected.

von Willebrand and Jürgens felt that their findings with the capillary thrombometer suggested that the pathogenesis of the disease can be assigned largely to a functional disorder of the platelets with reduced agglutinability and consequent deficient formation of platelet plugs. They therefore called the disease constitutional thrombopathy, a name which was later widely used, particularly in the German literature.

The authors distinguished constitutional thrombopathy from the disease, which had been described by Glanzmann (1918). In the latter disease clot retraction was regularly abnormal and the platelets showed considerable morphological changes not seen in the disease in the Åland bleeders.

Further studies on von Willebrand's disease and similar conditions

From the middle of the 1930s until the middle of the 1950s several cases of hereditary haemorrhagic diseases with prolonged bleeding time and normal platelet count were reported from Europe and U.S.A.

A large compilation of such cases has been published under the title of "Pseudohemophilia" by Buchanan

and Leavell (1956) (199 cases including 13 personal cases). Clot retraction is said to have been normal in the vast majority of these cases. Most of them were probably examples of von Willebrand's disease, this being the commonest of the hereditary haemorrhagic diathesis with prolonged bleeding time now seen at most large coagulation laboratories.

In the discussion of the pathogenesis, especially during the 1940s and 1950s, much space was given to the observations made by Macfarlane and described by him in his article: Critical Review: The mechanism of haemostasis (Macfarlane 1941). Under the name of athrombocytopenic purpura he reported cases of a hereditary bleeding disease with prolonged bleeding time and normal platelet count. He compared this form of bleeding disease with those described by von Willebrand and Glanzmann. He himself examined 5 such cases with capillary microscopy and found that the capillaries were both anatomically and functionally abnormal: they appeared to be tortuous and often bizarre, and they did not contract in a normal way after microtrauma. Macfarlane therefore considered the disease to be of vascular origin and rejected von Willebrand's and Jürgens theory supposing platelet deficiency as the main cause of the bleeding symptoms.

Findings like those described by Macfarlane have since been made in similar morbid conditions (O'Brien 1951, Alexander & Goldstein 1953, Schulman et al 1955, Singer & Ramot 1956 and others). Some authors, however, did not find the capillaries in so-called pseudohemophilia to be abnormal (Estren, Medal & Dameshek 1946, Jamra et al 1952, Braunsteiner 1955, Verstraete & Vandenbroucke 1955, R. Jürgens 1956, Sharp & Ellis 1960).

In 1947 Quick described a method for determining prothrombin in serum as a measure of prothrombin consumption. With this method he was able to demonstrate slight disturbances in the earlier phase of coagulation, disturbances which are not reflected in prolonged coagulation time.

In 1951 Jürgens and Forsius (R. Jürgens & Forsius 1951) found a reduced prothrombin consumption in 6 patients of the Åland family, while in other, less severe cases it was normal.

They felt that the low prothrombin consumption was probably due to disturbed function by a platelet enzyme involved in the formation or activation of plasma thrombokinase.

A platelet factor with this effect has since been known under the name of platelet factor 3.

Detection of low AHF and deficiency of an antibleeding factor in von Willebrand's disease

In the beginning of the 1950s improved methods were devised for determination of the antihæmophilic factor, which corrects blood coagulation in hæmophilia A and whose existence had been shown by Patek & Stetson (1936) and Patek & Taylor (1937) and others.

The most widely known method is the one described by Biggs & Douglas (1953) as the thromboplastin generation test. This test made it possible readily to distinguish hæmophilia A from hæmophilia B and to estimate the content of the antihæmophilic factor (AHF).

The same year, *i.e.* in 1953, three reports appeared of cases with decreased AHF in bleeders with a prolonged bleeding time despite normal platelet count, *i.e.* with a clinical picture often described as characteristic of pseudohæmophilia. The reports were given by Alexander and Goldstein (1953), Larrieu and Soulier (1953) and Quick and Hussey (1953). Similar findings in this type of disease were later described by *e.g.* van Creveld *et al.* (1955), Schulman *et al.* (1955) and Singer and Ramot (1956).

In 1956 I.M. Nilsson *et al.* (1956) described a case (Birgitta) and its treatment with AHF and Fraction I—O. The condition was entitled female hæmophilia because the girl had been found to have a considerably reduced content of AHF — down to 1–5 % of the normal. But the condition differed from classical hæmophilia in two respects: it was seen in a female, and the bleeding time was noticeably prolonged. The patient had previously had several episodes of bleeding such as nose bleeding, gingival bleeding and bleeding from the sockets after tooth extractions. From menarche the disease had assumed a serious character with life-threatening menorrhagia. Blood transfusions produced only temporary improvement of the blood values and finally caused severe symptoms of sensibilisation.

The authors therefore decided to try the effect of human Fraction I—O from Cohn's Fraction I (Blombäck & Blombäck 1956), a preparation in which the antihæmophilic globulin activity of the original plasma was almost completely preserved.

A test dose of Fraction I—O corresponding to the AHF-content of 2,500 ml blood "promptly controlled the bleedings from the gingiva, from a pin prick in the ear and from the uterus". The coagulation time and the bleeding time became normal and the AHF-content of the plasma increased to 55%. After 48 hours half of the injected AHF-activity was still demonstrable.

Four days later the patient received another dose of Fraction I—O, and the next morning hysterectomy was performed without any increased bleeding tendency.

During the following years Nilsson and co-workers found several similar cases. By 1959 they had examined in all 26 patients belonging to 20 different families. The females were affected to the same extent as men (Nilsson, Blombäck & Blombäck 1959).

Treatment with Fraction I—O was tried on several of these patients in association with episodes of acute bleeding or at operation: such treatment invariably had a favourable effect with an increase of the AHF-content and shortening of the bleeding time, often to normal values. Also the clinical results were very satisfactory.

Fraction I—O contains not only AHF, but also fibrinogen in high concentration. Administration of purified fibrinogen produced no effect on the AHF-level or bleeding time of the patients. Purified AHF: Fraction I—1 A (Blombäck and Blombäck) had no effect on the bleeding time either. On the other hand, AHF-free Fraction I—O prepared from plasma of patients with severe hæmophilia A shortened the bleeding time.

The authors (Nilsson, Blombäck & von Francken 1957) concluded: "Taken together these observations could indicate that the prolonged bleeding time in this syndrome is caused by deficiency of a "vascular factor", which is present in Fraction I—O and not identical with AHF or fibrinogen".

As for the increase in AHF-activity, it was found to exceed that expected from the amount of AHF given with Fraction I—O (Nilsson, Blombäck & Blombäck 1959). The highest activity level was not noted immediately after the infusion, but after several hours. It then gradually fell and reached normal level after several days. It was also found that Fraction I—O from hæmophilia A-patients with an AHF-content of only 1–2% raised the AHF-level in one patient from 6 to 19 % of normal value. It was therefore concluded that the above-mentioned factor not only affected the bleeding time, but also stimulated the production of AHF.

The effect of treatment on the bleeding time was of shorter duration than that on the AHF-production and a markedly prolonged bleeding time had often returned to original values within less than a day (Nilsson, Blombäck & Blombäck 1959).

Studies of the platelets of the patients revealed no platelet defect. Even platelet factor 3 was found to be normal (Nilsson, Blombäck & von Francken 1957).

Further, infusions of washed platelets from normal persons were given, but without any effect on the bleeding time.

On careful examination of the families the authors found that the patients with a tendency to bleeding always had one parent with reduced AHF-content, while the other parent and his or her family had normal values. It was found that the AHF-deficiency was inherited as an autosomal dominant gene (Nilsson, Blombäck & von Francken 1957).

The bleeders traced in Sweden resembled those belonging to the large families of bleeders in Åland in respect of heredity, symptoms and prolonged bleeding time. But in the Swedish cases, in contrast with those from Åland, platelet function was not impaired.

In 1957 Nilsson and co-workers therefore went to Åland and studied the patients belonging to the Åland family, including some who had been examined 25–30 years previously by von Willebrand himself (Nilsson et al. 1957). They found the AHF-values to be decreased, but the platelet factor 3 to be normal. One of the patients from Åland was given Fraction I—O, "which controlled the coagulation defect and the bleeding time". These investigations had thus for the first time shown that the disease, which in several quarters had been described as being characterised by a reduced AHF-content and prolonged bleeding time, was identical with von Willebrand's disease.

The same year Jürgens et al. also showed the AHF-content often to be reduced in the Åland-bleeders (R. Jürgens et al. 1957). The deficiency of this factor has since been regarded as a characteristic, if not an obligatory feature of the disease.

Fraction I—O was afterwards used widely by Nilsson and Blombäck in the treatment and prophylaxis of severe forms of von Willebrand's disease. In mild cases and in less acute situations it proved sufficient to use fresh plasma or freshly frozen plasma (Nilsson 1965).

The results obtained on administration of different sorts of plasma and plasma fractions in von Willebrand's disease have since been widely confirmed by several researchers (Cornu et al. 1961 and 1963, van Creveld et al. 1963, Borchgrevink et al. 1963, Barrow and Graham 1964, Ikkala, Myllylä & Nevanlinna 1964, H. Perkins 1967 and others).

Among others, Cornu and co-workers have shown that haemophilia A-plasma, like normal plasma, contains the factor, that stimulates AHF-production in von Willebrand's disease. But no such effect is produced by transfusion of plasma from a patient with von

Willebrand's disease to one with haemophilia A.

These observations have given rise to much speculation on AHF-synthesis in the two diseases, seen largely from a genetic point of view.

Graham and Barrow published investigations (Graham 1959, Graham, Barrow and Roberts 1965) based partly on the Swedish von Willebrand-series. They pointed out that in many cases prolonged bleeding time and reduced AHF-content are not seen together and that the symptoms may perhaps be inherited by different genes.

Investigations of von Willebrand's disease since the latter half of the 1950s

During the 1950s and 1960s von Willebrand's disease received increasing attention. Cases were reported from most countries in Europe as well as from different parts of the world, such as Chile (Larrain and Bancalari 1965), South Africa (Gomperts et al. 1969), India (Kasliwal et al. 1966), Japan (Yamada et al. 1965) and Australia (Castaldi et al. 1967).

The frequency of the disease is now approaching or exceeding that of haemophilia (Horowitz & O'Leary 1965, Quick 1967:a, J. Jürgens 1969).

The increase in the frequency of recognised cases is due to some extent to the use of Ivy's method for determining the bleeding time (Nilsson, Magnusson & Borchgrevink 1963, Silwer & Nilsson 1964, Ascari, Barbieri & Gobbi 1964, Cornu 1965, Abildgaard et al. 1968 and others). This method, especially Borchgrevink and Waaler's (1958) modification of it, has proved sensitive and valuable and has revealed an increased bleeding tendency in many mild cases with a normal bleeding time with the Duke technique.

Cases of a hereditary bleeding disease with prolonged bleeding time, as in von Willebrand's disease, have been reported, but with normal values for AHF and a low content of haemophilia B-factor (Achenbach & Klesper 1957, Combrisson-Le Bolloch, Debray & Benhamou 1957, Soulier & Larrieu 1957, Gugler 1960, Blackburn et al. 1962, Mey & Panzram 1962, Winckelmann & Walther 1964, Wake & McClure 1965, Schweiberer, Wendlberger & Licht 1966, Özsoylu & Corbacioglu 1967:b).

In the 1960s attention was directed to, above all, platelet dysfunction.

Especially German investigators have given attention to the supposed deficiency of platelet factor 3. The idea of a true deficiency has been more or less re-

placed by the assumption of an inhibited release of the factor in question (Johnson, Monto & Caldwell 1958, Landbeck & Uathavikul 1959, Eriksson et al. 1961, Winckelmann & Walther 1964 and others).

Among others, Eriksson and co-workers have found electron microscopic changes in the granules of platelets, which they believe to constitute the morphological basis of the reduced platelet factor 3 activity.

In the Anglo-American, Scandinavian and French literature much interest has been devoted to a reported decreased platelet adhesiveness and platelet aggregation in von Willebrand's disease.

The methods for determining platelet adhesion to glass have been improved by Hellem, who pumped citrated blood through plastic tubes filled with glass beads (Hellem 1960). Hellem examined a few patients with von Willebrand's disease, but found no certain decrease in platelet adhesiveness. Later, however, Salzman (1963) modified the method by inserting the tube with the glass beads between the needle for venous puncture and a vacuum tube containing EDTA. In this method, directly after puncture the platelets pass over the beads before they come into contact with the anticoagulant. With this set-up the flow rate is increased. Salzman regularly found the platelet adhesiveness to be decreased in patients with von Willebrand's disease. Salzman's findings have since been confirmed by various workers (Strauss & Bloom 1965, Bennet & Dormandy 1966, Lemoyne & Larrieu 1967, H. Perkins 1967 and Abildgaard et al. 1968 and others).

Borchgrevink (1960) in Norway, who used an "in vivo-method" for measuring platelet adhesiveness found results compatible with Salzman's ones.

The observations made have since been related to the anti-bleeding factor in normal plasma, demonstrated by Nilsson et al. It has been thought that it is via the platelets that this factor exerts its action by influencing their adhesiveness and aggregation (Ödegaard, Skålhegg and Hellem 1964:b, Owren 1965).

Especially French researchers (Larrieu et al. 1968, Meyer & Larrieu 1970) have found that administration of normal plasma and plasma fractions to patients with von Willebrand's disease causes a correction of the decreased platelet adhesiveness parallel with the suppression of the bleeding tendency.

In 1960 Hellem described a factor R, which influences adhesiveness of platelets in normal plasma. This factor has since been identified by Gaarder et al. (1961) as ADP.

Norwegian and French researchers have studied the effect of ADP also on platelet aggregation and reported an abnormal reaction to ADP in low concentrations in patients with von Willebrand's disease (Ödegaard, Skålhegg & Hellem 1964:a, Vainer & Caen 1964). Some of these experiments were repeated on a large series of patients with von Willebrand's disease by Cronberg, Nilsson and Silver (1966), who, however, were unable to find any difference in the reaction of these patients and normals.

Thereapeutically, many investigators have used Pool's cryoprecipitate, which is said to have essentially the same effect as Fraction I—O (Bennet & Dormandy 1966, Castaldi et al. 1967, Dana 1967, H. Perkins 1967, Abildgaard et al. 1968, Walker & Dormandy 1968, Rizza & Biggs 1969, Komp, Nolan & Carpenter 1970).

Moreover, various hormone preparations have been tried, *e.g.* cortisone and related steroids (B. Jacobsson 1953, 1957, Schulman et al. 1956, Bernard et al. 1957, Cornu et al. 1961, Lemoyne & Larrieu 1967, Ponka, Monto & Welborn 1967 and others). Further, in the treatment of bleeding from the female reproductive organs preparations of different types of sex hormones have been used, even "p-pills" (Achenbach 1960, Barrow & Graham 1964, Bonechi & Pasero 1964, Akman et al. 1965, Özsoylu & Corbacioglu 1967:b, van Crevald & Shellekens 1969 and others).

Thus, especially in the last decades, von Willebrand's disease has received increasing space in the literature. The combination of prolonged bleeding time and deficiency of one of the widely known clotting factors, AHF, is difficult to explain. The so-called von Willebrand-factor, which is found in Fraction I—O, can be postulated from its known effects. The chemical nature and mechanism and mode of action of this substance is, however, not properly understood. Its possible significance in such diseases as thrombosis and arteriosclerosis has also been discussed (Owren 1965, Silver, Cronberg & Nilsson 1967). As for the significance of platelets in the pathogenesis of von Willebrand's disease, opinions still differ.

Wide experience has accumulated through the years as to the clinical picture of the disease, its symptoms, risk of bleeding in various situations, diagnosis, possibilities of treatment and prognosis. Utilisation of this experience should prove of great help to physicians in the recognition and treatment of cases encountered in their practical activity.

MATERIAL AND METHODS

MATERIAL

The material consisted of all patients with a firm or highly probable diagnosis of von Willebrand's disease and seen at the Coagulation laboratories in Malmö, Stockholm or Gothenburg in the years 1956–1967.

Inquiries were made into all of the families of the patients included in the investigation. When possible, laboratory studies were made of the closest relatives of the probands, particularly their parents, siblings and children. The material presumably includes all known cases of von Willebrand's disease in Sweden up to the end of 1967. The diagnosis requires special laboratory facilities, at present available only in Malmö, Stockholm and Gothenburg.

The investigation included a careful inquiry into the probands history regarding bleeding symptoms and the information obtained was, as a rule, supplemented by data from earlier hospital records in those cases in which the patient had sought medical advice or had been admitted to hospital because of their haemorrhagic symptoms.

In most cases, and particularly in probands, a complete investigation was made of the patient's bleeding and coagulation status.

Examination of relatives of the probands was often limited to determinations of the bleeding time according to Duke and Ivy and of the AHF.

The probands were all examined several times and at least on one occasion during a period when they were not bleeding. Relatives were also often examined more than once, especially in doubtful cases.

METHODS

Interest was focused mainly on determinations of: AHF

Bleeding time according to Duke and Ivy

Platelet adhesiveness according to Salzman

AHF-determinations

Blood sampling. — Venipuncture was performed with sharp, wide needles with a polished bore (caliber

1.2–1.6). The first few millilitres were discarded, and the blood was allowed to flow directly through the needles into the tubes.

The blood was collected with the silicone technique. Citrated plasma (one part 3.8% trisodium citrate solution $\times 2$ H_2O + 9 parts blood) and serum were prepared by methods, described previously by Nilsson et al. (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck, Thilén & von Francken 1959 and Paraskevas, Nilsson & Martinsson 1962). The blood was immediately centrifuged at 2,300 g for 25 minutes at room temperature. Plasma was withdrawn by means of siliconised pipettes and immediately frozen in plastic tubes at -20° — $-60^\circ C$.

The plasma antithaemophilic factor (AHF or factor VIII) was assayed on platelet-rich haemophilia A-plasma (AHF-content $< 1\%$) in a recalcification system, in which the ability of the citrated control plasma and of the test plasma to correct the prolonged recalcification time of citrated haemophilia A-plasma was compared. The haemophilia A-blood was drawn with the silicone technique and centrifuged without delay at about 700–1,000 g for 10 minutes. It was checked that haemophilic plasma contained at least 200,000 platelets per cu.mm. The plasma was then distributed in plastic tubes and stored at -20° — $-60^\circ C$ (it was usually used within 2 weeks). This method has been described and commented upon by Nilsson et al. (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck, Thilén & von Francken 1959). The plasma of patients with von Willebrand's disease was assayed at dilutions 1:20, 1:50 and 1:100.

As 100% standard for the assay of AHF in the patients use was made of mixed citrated plasma from 10–20 normal subjects collected at about the same time (at most an interval of 5 days) as the test specimen.

Normal values in 20 healthy men and women aged 20–40 years ranged from 60 to 160% with a mean of $100 \pm 17.5\%$. The AHF-content in a group of 10 healthy women past the menopause ranged from 76 to 199% with a mean of 139%.

The mean error of the method at different AHF-levels had been determined:

Table 1

Mean error at different AHF-levels

AHF-level (%)	Standard error
0,1 – 1	$\pm 0,1 - \pm 0,3$
2 – 3	$\pm 0,6$
4 – 6	$\pm 1,4$
15 – 25	$\pm 4,5$
30 – 40	$\pm 5,2$

Bleeding time

This was determined by

1) The method of Duke using standardised haemolets (Dade Reagent, Inc. Miami, Florida, U.S.A.). Determinations were mostly performed on both ears. Normal range 1 to 5 minutes.

2) The method of Ivy (Ivy, Nelson & Bucher 1941), as modified by Borchgrevink and Waaler (1958) and also described by Nilsson, Magnusson and Borchgrevink (1963). An arm cuff was wrapped round the upper arm and inflated to 40 mm Hg. Three transverse incisions, 1 mm deep and 10–14 mm long, were made on the volar side of the forearm with a surgical blade (Gillette Surgical Blade E). The blood shed was gently and carefully absorbed at about 15 second intervals with a filter paper until the bleeding stopped. The mean of triple determinations in 35 volunteers examined at the coagulation laboratory in Malmö was 9.5 minutes (range 5–15.5 minutes) and in a later investigation (Cronberg 1968) of 70 volunteers 10.0 minutes (range 5–20 min.), S.D. ± 3.1 and standard error ± 0.37 . The bleeding time exceeded 15 minutes in 2 out of the 70 persons.

The corresponding mean found in Stockholm was somewhat lower, and the bleeding time in normal persons did not exceed 12 minutes.

Platelet adhesiveness

The original method of Salzman (1963) was used with a thin needle (caliber 0.14–0.2). Fresh blood was drawn directly from a vein through a short column (11–13 cm) of glass beads into a vacuum tube with EDTA. The tube should be filled with about 5 ml in 40–50 seconds. Normal value according to Salzman 20–60%. The normal value at the coagulation laboratory in Malmö based on 34 volunteers, aged 20–30 years, is 33% with S.D. ± 17.0 and standard error ± 2.9 .

At estimation of platelet adhesiveness the platelets were counted with macro-method. For this purpose

Hellem's modification (Hellem 1960) of Nygaard's method (Nygaard 1933) or Björkman's method (1959) were used.

Other tests

Other tests concerning bleeding and coagulation-status on persons included in the present investigation are listed below:

Coagulation time in glass tubes. Modified method of Hedenius (1936).

Coagulation time in plastic tubes, measured in the way described by Cronberg (1968).

Recalcification time of plasma (Nilsson et al. 1962).

Platelet counts (Kristensson 1928–29 or Björkman 1959).

Haemophila B – factor (= f IX) (Nilsson et al. 1962).

Prothrombin consumption test (Biggs and Macfarlane 1957).

Prothrombin + factor VII + factor X. The P & P method of Owren and Aas (1951).

Factor V (Wolf 1953).

Fibrinogen (Blombäck and Blombäck 1956 or Nilsson and Olow 1962).

Fibrinolysis (Blombäck and Blombäck 1956, Bergström et al. 1960 or Nilsson and Olow 1962).

Platelet adhesiveness according to Hellem (Hellem 1960).

Anticoagulants (Lewis, Ferguson and Arends 1956, Laurell and Nilsson 1957 or Hedner and Nilsson 1971).

Capillary fragility test, as described by Hedner and Nilsson 1971.

Platelet aggregation, measured in the way described by Karaca and Nilsson 1972.

Platelet factor 3, measured in the way described by Karaca and Nilsson 1972.

AHF-CONCENTRATES FOR TREATMENT

For treatment with AHF-concentrates human Fraction I–O, containing AHF, prepared by the glycine method of Blombäck, B. and Blombäck, M., was used.

The preparations were originally made at Karolinska Institutet, and every batch was made from 1,400–1,600 ml of fresh plasma, obtained from 8 blood donors. This yielded about 3 g. of Fraction I–O, which was dissolved in two bottles of 100 ml (100 ml = 1 dose of AHF). This preparation had an activity of 5–8 times that in normal plasma. The purification of AHF per mg protein in Fraction I–O

compared with fresh human plasma was about 20 times. The yield of AHF in Fraction I—O constituted 70—100% of the AHF-content of the original plasma (method described in detail by Blombäck & Blombäck 1956, Blombäck, Blombäck, Jorpes & Nilsson 1960 and Jorpes et al. 1962). A good correlation exists between *in vitro* and *in vivo* yield.

Since 1967 AB Kabi has taken over the production of AHF-containing Fraction I—O (F I—O). They use

for each batch about 25 liters of blood from about 125 blood donors. AB Kabi use mainly frozen plasma as starting material. Larger batches, sterile filtering and deep freezing have resulted in a somewhat less good yield. 100 ml F I—O (1 dose) now has, as a rule, the AHF-activity of only 250—300 ml fresh plasma. Such large scale manufacture of the preparation has also resulted in a weakening of its effect on the bleeding time.

CRITERIA

von Willebrand's disease demonstrated

in probands

The criteria used for the diagnosis of von Willebrand's disease in the probands in this investigation were as follows:

- 1) History of bleeding tendency with severe or often repeated abnormal bleedings that could not be explained by any other disease.
- 2) Reduced AHF $< 65\%$, for females in the menopause $< 75\%$.
- 3) Bleeding time according to Duke more than 5 minutes or according to Ivy, more than 15 minutes (in Stockholm more than 12 minutes).

In most cases diagnosis was confirmed further by

- 4) Occurrence of similar bleeding disease in the patient's family.
- 5) Decreased platelet adhesiveness according to Salzman.
- 6) Retarded AHF-increase and shortening of the bleeding time after infusion of Fraction I--0 and/or fresh plasma.

in relatives

In relatives of the probands the diagnosis of von Willebrand's disease was made if they met two of the three first mentioned criteria (1-3).

In cases where the bleeding time had been determined only according to Duke, a low AHF-content was regarded as sufficient for the diagnosis in relatives:

- 1) if the AHF-level was $< 65\%$, provided that the person examined had children as well as siblings

- or parents with a firm diagnosis of the disease and could thus be regarded as a carrier of the gene.
- 2) if the AHF-level was $< 50\%$.

von Willebrand's disease excluded

von Willebrand's disease was excluded in:

- 1) Persons without a positive bleeding history and with AHF $\geq 65\%$ and the bleeding time according to Duke ≤ 5 minutes and according to Ivy ≤ 15 minutes (in Stockholm ≤ 12 minutes).
- 2) Persons who had mild bleeding symptoms but normal values for AHF and bleeding time.
- 3) Persons without a positive bleeding history but with single mildly pathological values for AHF (50-64%) or for bleeding time according to Duke (6-10 minutes) or Ivy (16-20 minutes).

Intermediate results

Persons who could not be defined as affected or healthy according to these criteria were referred to a special group under the name "intermediate results".

Type: Severe or mild

Patients with a firm diagnosis of von Willebrand's disease were grouped according to whether the disease was severe or mild. The disease was said to be severe if it was characterised by pronounced bleeding manifestations with a bleeding time according to Duke of on the average more than 30 minutes and a plasma AHF-activity of less than 20% on at least one occasion.

RESULTS

The results are given in tabular form, (Table 2), where each family is described separately. The table contains data on the histories and values for the bleeding times according to Duke and Ivy, AHF-content in the blood and platelet adhesiveness according to Salzman. Other results of the bleeding and coagulation status did not show any remarkable deviation from normal. Only in single cases was the platelet count decreased or was a circulating anticoagulant demonstrated. This was then given in the column for remarks.

The Case reports (page 58) describe the most pronounced bleeding symptoms and those referred to in the text in order to illustrate their character and severity. When possible data are also given on the patient's age at the time of such bleedings.

A pedigree is given for each family.

Abbreviations

The following abbreviations were used in the tables:

Sex

M	= male
F	= female

Type

Sv	= severe von Willebrand's disease (see page 13)
Mi	= mild von Willebrand's disease (see page 13)
Int	= intermediate results (see page 13)
N	= normal (see page 13)

When the severity of the disease could be judged only from the patient's history, the classification is given in brackets: (Sv), (Mi), (Int).

Bleeding symptoms

In captions

N	= nose-bleeding
G	= gingival bleeding
TS	= tooth shedding with haemorrhage
TO	= traumatic oral or lip-bleeding
T	= tonsillar or pharyngeal bleeding
E	= ear bleeding
GI	= gastro-intestinal bleeding (not bleeding from haemorrhoids)

UT
M
Part.
O
EH
P
Tr

J
TE
Misc
Op.
Sum

Miscellaneous

Boil	= bleeding from boil
Ceph. haem	= cephalic haematoma
Coit	= coital bleeding
Dent. abscess	= bleeding from dental abscess
Eye	= eye bleeding
Fl. o. m	= bleeding in floor of mouth
Fract	= bleeding from fracture
Haemorrh	= bleeding from haemorrhoids
Hpt	= haemoptysis
Icr	= intracranial bleeding
I. m	= intramuscular or deep subcutaneous bleeding
Max	= maxillary bleeding
Miscarr	= bleeding at miscarriage
Oes	= oesophageal bleeding
Pl	= intrapleural bleeding
Subarachn	= subarachnoid bleeding
Tooth erupt	= bleeding at tooth eruption
Umbil	= umbilical bleeding
Vag	= vaginal bleeding (menstruation and metrorrhagia excepted)

Operations

Ab	= abortion
Abd	= explorative abdominal operation
App	= appendectomy
Chol	= cholecystectomy
Curett	= uterine curettage

Dent. abscc	= operation of dental abscess
Ear	= otological operation
Ex. ut	= operation of extra-uterine pregnancy
Fract	= operation of fracture
Fren. ling	= operation of frenulum linguae
Gastr	= gastric operation
Gyn	= small gynaecological operation
Haemorrh	= operation of haemorrhoids
Hernia	= operation of inguinal hernia
Hy	= hysterectomy
Icr	= intracranial operation
Intest	= operation of intestine
Joint	= operation or puncture of joint
Lipoma	= operation of lipoma
Lymph node	= lymph node biopsy
Mam	= operation of mammae
Max	= puncture of maxillary sinus
Meato	= meatotomy
Myom	= myomectomy
Nose	= nasal operation
Oes	= operation of oesophagus
Ov	= operation of ovary
Pimpl	= incision of pimples
Pl	= pleural puncture or thoracocentesis
Prost	= prostatectomy
Salp	= salpingectomy
Sect. caes	= sectio caesarea
Skin	= skin operation
Skin trspl	= skin transplantation
Tartar	= removal of tartar
Thyr	= subtotal thyroidectomy
To	= tonsillectomy
Trach	= tracheostomy
Vacc. scar	= operation of vaccination scar
Veg. ad	= removal of adenoid vegetations
Vertebr	= operation of intervertebral hernia
Ves. stone	= operation because of vesical stone
Wart	= extirpation of wart

Grading of bleeding symptoms

The bleeding symptoms in the tables are graded according to severity as 1, 2 or 3. These signs denote essentially as follows:

1 Bleedings, which appeared to be more pronounced than in normal persons but were not severe or otherwise remarkable. They did not require any

special measure and did not cause known anaemia.

Example:

Profuse or recurrent nose bleeding. No measures. Profuse or regularly recurrent gingival bleeding during toothbrushing. — Mild spontaneous gingival bleeding.

Profuse menstrual bleedings for a long time. No known anaemia. No treatment.

Bleeding at or after delivery, described by patient as profuse. No data on amount of blood lost. No known anaemia. No treatment apart from routine methergin-injection at expulsion of the foetal head.

Bruises after trivial or unknown trauma.

Profuse or prolonged bleeding from small wounds. No treatment.

Profuse bleeding after tooth extraction. No treatment.

Profuse postoperative bleeding, reported with certainty by patient but not mentioned in hospital records.

2 Bleeding symptoms which were severe or otherwise remarkable or which required special haemostatic measures. They often caused anaemia. No blood transfusions given.

Example:

Nose bleeding treated with cauterisation or tamponade.

Spontaneous gingival bleeding when patient awoke in the morning with blood on pillow.

Gastro-intestinal bleeding with considerable blood loss, often with demonstrable anaemia.

Abundant or prolonged urinary tract bleeding. Gross haematuria of unknown cause.

Profuse menstrual bleeding for which patient sought medical advice and treatment. Anaemia usually demonstrated.

Bleeding at delivery with loss of more than 600 ml blood or with demonstrated anaemia (not demonstrable before parturition) or which required special haemostatic measures.

Ovarian bleeding with very probable diagnosis.

Large or numerous haematomas for which patient sought medical advice and sometimes received treatment.

Traumatic bleeding, abnormally profuse for nature of injury and requiring special haemostatic measures.

Joint bleeding with very probable diagnosis.

Bleeding after tooth extraction which required treatment, *e.g.* suture or tamponade.

Bleeding at or after operation which was noted in the records as remarkable.

- 3 Bleeding requiring blood transfusion or being the cause of the patient's death, which is then stated in column for remarks.

The grading of the bleeding is, of course, only approximate. Many factors were involved of which mention might be made of the following:

Evaluation depended largely on the patient's subjective opinion. Several data on the unexamined relatives of the probands were obtained from a third person. The occurrence of treatment often decided the evaluation of the severity of bleeding. It is, however, obvious that formerly patients sought medical advice much less often than nowadays and the indications for treatment vary from one physician to another. Anaemia, when reported, was confirmed by data on the Hb, but determination of Hb has many inherent sources of error and depends on the widely varying precision with which it is determined. — Reported blood transfusions could almost always be confirmed by examination of the records. The number of blood transfusions is naturally not a *very* reliable measure of the severity of bleeding, but it is not without value.

Other signs

Other signs used in the columns for bleeding symptoms were:

- This sign has been used at deliveries, miscarriages, fractures, tooth extractions and operations, which have occurred or been performed without abnormal bleeding.

- 0 This sign has been used

a) in column for parturition regarding females above 15 years, who reported that they had never been delivered

b) in column for tooth extractions regarding patients in whom no tooth extraction had been performed.

- t* This sign was used when specific therapy or prophylaxis had been given with fresh plasma and/or Fraction I—O. *t* before figures denotes prophylaxis and *t* after figures denotes treatment of bleedings.

Examination values

In columns for laboratory values the abnormal values for bleeding times, AHF and platelet adhesiveness according to Salzman are given in italics.

The following values were regarded as abnormal:

Bleeding time according to Duke	> 5 minutes
Bleeding time according to Ivy	> 15 minutes
Bleeding time according to Ivy in Stockholm	> 12 minutes
AHF	< 65%
AHF in menopausal women	< 75%
Platelet adhesiveness according to Salzman	< 20%

- s When the bleeding time according to Ivy was determined in Stockholm it is marked with s.

- o When samples for determination of AHF were sent to the coagulation laboratory from another place for examination this is denoted by o.

The menopause is noted when it was thought to be of particular interest, especially for classification of the person as affected, "intermediate" or normal (higher normal value for AHF in women in the menopause).

Table 2
Abbreviations and signs explained on page 14-16.

Family 1

Family	Bleeding history														Examinations														
	Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF % S _z %	Remarks	
V: 5 BT	F	1939	Sv		3	3					3+	3	0	2	1	2						3	Gastr t- Hy t 2 Curett 2	+++	5/56 6/56 10/57 10/67 10/68	>60 >30 >60 >30 >90*	1-5 4 4		
	III: 5 EK	F	1898	Sv		2	1					2	0	1	1							1	Curett ?	+++	4/39	>90*			7 * test at lo- cal hosp.
	IV: 7 GJ IV: 9 ST	M F	1893 1899	Mi Mi								3	2	---								1	Curett -	+	56 56	3 6			5 10 55 62
IV: 15 OJ IV: 6 HJ IV: 5 KAT IV: 8 EB IV: 10 KJ IV: 11 EJ IV: 14 AA V: 3 KB	M F M F M F F F	1915 1892 1894 1897 1901 1904 1911 1931	Mi Int. N N N N N N	1																		-		56 56 56 56 56 56 56	2 15 86 5 5 8 4 7 3			48 ≥100 100 90 100 100	

Table 2 (continued)

Family 2

		Bleeding history															Examinations											
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 YL	F	1941	Sv	3		1		2		3		3	/3	3	1		3				1	Ov3 Ov13	++	8/56 8/61	>60 >60		3 4	
III: 3 GL	F	1950	Sv	1	2	3	3r					3r	0								0		++	10/65 56	14 >60		2 3	
II: 5 WM	M	1899	Mi	1																	-		-	56	1		21	
II: 11 HN	F	1907	Mi	1	1							1-		1				1			-	+	56	4		52		
II: 14 KM	M	1911	Mi																		-		56	2		86		
II: 15 TM	M	1911	Mi																		-		56	1		21		
II: 16 IL	F	1914	Mi																		-		56	4	7	21		
III: 1 GRK	M	1946	Mi	1	1																-		8/56	3		37		
III: 5 ML	F	1924	Mi	1	1																-	+	9/56	4			75	
III: 13 LM	M	1941	Mi		1										1	1					-	+	56	8		32		
III: 10 PN	M	1936	Int.	1																	0	-	58	3		33		
I: 1 FPL	M	1890	N																			-	58	3		59		
I: 2 FL	F	1885	N																			-	56	1		104		
II: 2 KL	M	1914	N																			-	56	5		87		
II: 3 RDK	F	1917	N																			-	56	3		85		
II: 4 HM	M	1897	N																			-	56	1		80		
II: 7 FM	M	1902	N																			-	56	4		89		
II: 9 SM	M	1904	N																			-	56	2		90		
II: 10 JM	M	1905	N																			-	56	3		95		
II: 13 MM	F	1909	N																			-	56	3		85		
II: 18 MM	F	1916	N									0										-	56	7	10		95	
III: 6 RM	M	1928	N									-		1								-	56	4		93		
III: 7 IG	F	1929	N												1							-	58	2		120		
III: 8 TBS	F	1931	N																			-	58	3		120		
III: 9 BH	F	1931	N								1											-	58	3		116		
III: 11 RM	F	1935	N																			-	58	3		132		
III: 12 BM	F	1943	N																			-	58	2		88		
III: 14 OM	F	1947	N																			-	58	3		115		
																						-	58	4		70		

Table 2 (continued)

Family 3

Case		Sex	Born	Type	Bleeding history												Examinations												
					N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 MH					F	1938	Sv	3	2	2	3	3	3	0	2				Coit 2	2	+	+	+	9/56 9/56 10/68	> 25 > 30	6 14 > 30		12	
II: 9 MH					F	1905	Mi							--			1	1	+				56 56 56	4 3 4	48 94 100				
II: 3 RS					F	1890	N																56 56	4 4	100				
II: 4 NH					M	1894	N																56 56	2 2	100				
II: 6 SH					M	1895	N																56		86				
II: 7 EH					F	1900	N																56	10	90				
II: 8 AH					M	1902	N																56	1	98				
III: 2 KH					F	1902	N							---									56	9					

Family 4

		Bleeding history													Examinations												
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IV: 1 GB	F	1940	Sv	1	3	2	3		2	3	0	2		3		3	3	Vag 2 lcr 3*	3		++ +	11/56 2/57 1/61	>60 >60 60		5 5 4		* fatal
IV: 2 AB	F	1943	Sv	3*	3	3											2	Boil 2	3	Pimpl 2	++ +	43- -51	>10** >15**				* fatal ** test at lo- cal hosp.
III: 3 AB	F	1912	Mi									---						Mis- carr -	-	Gyn 1	-	12/56	1		45		
III: 5 NAH	M	1905	Mi																	Curet -					43		
III: 6 KB	F	1914	Mi																		-	12/56	4		55		
IV: 4 YH	F	1944	Mi												1						-	12/56	7		46		
IV: 5 TH	M	1947	Mi	1																	+	1/59	6		33		
IV: 7 LB	M	1939	Mi																		-	12/56	3		38		
II: 6 AH	M	1873	Int.																		-	12/56	4		56		
II: 5 SH	F	1881	N																		-	12/56	2		128		
III: 1 DD	F	1912	N																		-	12/56	2		98		
III: 2 SB	M	1904	N																		-	12/56	10		95		
																							2	1	8		
IV: 3 HCB	M	1948	N																		-	12/56	2		106		
IV: 6 CH	M	1948	N																		-	12/56	6		98		
IV: 8 AMB	F	1941	N																		-	12/56	6		107		
IV: 9 HB	M	1945	N																		-	12/56	4		86		

Family 5

Bleeding history																				Examinations								
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
IV: 1 WP	M	1947	Mi	3	1									1		1			2		+	+	1/57 10/60 12/66	4 >40 16		15 47 29		
II: 8 EP	F	1887	Mi								---	---	---						1		-	-	57	1	21	38	6	
III: 1 EP	M	1910	Mi						2			---	---						-		+	+	57	5		42		
III: 2 AE	F	1912	Mi	1	1						---	---	---						-		+	+	57	2		52		
III: 5 PP	M	1919	Mi	1	1									1		1			1	Lipoma 2 Myelo- graphy /-	+	+	1/57 10/60	>30 43		25 23		
III: 6 KS	F	1922	Mi								--	--						Mis- carr -	-		-	-	12/66 57	3 7	25	21 51	9	
III: 8 MBP	F	1927	Mi								0							-			-	-	57	1		45		
II: 1 PP	M	1881	N																-		-	-	57	1		150		
II: 7 WJ	F	1880	N																-		-	-	57	1		150		
III: 3 EF	F	1914	N								---	---	---						-		-	-	57			118		
III: 4 EB	F	1917	N						3*			--	--						-		-	-	57	1		180		* Ruptured myoma
III: 9 BP	F	1930	N																-		-	-	57	2		75		
III: 10 MLj	F	1897	N																-		-	-	57	5		150		
III: 17 JP	F	1920	N																-		-	-	57	3		76		

Family 6

Bleeding history																				Examinations							
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IV: 2 RF	M	1955	Sv	2	2	2t	3						2		3t		2t	l.m. 2t	3	-	++ +	1/57 9/67	> 240		5 17		
II: 16 FOK	M	1888	Mi	1															-	Prost 2	+	9/69			6	10	
III: 2 MO	F	1918	Mi								0								-	App- Hy- Ov + Myom 3	+	2/57 2/57	9 2		38 43		
																			-	Curet -							

Table 2 (continued)
Family 6 (continued)

Bleeding history																Examinations												
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy	AHF	Sz	Remarks
																									min.	%	%	
III: 3 GS	F	1921	Mi									0									2		2/57	1		42		
III: 5 KFK	M	1924	Mi																	-			2/57	4		34		
III: 6 EF	F	1930	Mi																				2/57	2		25		
I: 4 SK	F	1884	N												1						Curet-		2/57	2		93		
II: 1 SF	M	1901	N																				2/57	1		143		
II: 3 TF	M	1909	N																				2/57	2		90		
II: 5 GF	F	1905	N																				2/57	4		78		
II: 7 NEK	M	1908	N																				2/57	2		79		
II: 8 ÅK	M	1912	N																				2/57	1		74		
II: 9 HK	M	1914	N																				2/57	2		132		
II: 11 HK	M	1925	N																				2/57	2		105		
II: 22 AMK	F	1886	N																				2/57	1		87		
II: 23 EK	F?	1888	N																				2/57	5		97		
III: 1 YF	M	1925	N																				2/57	2		88		
III: 4 EE	F	1922	N																				2/57	5		104		
IV: 1 EF	M	1948	N																				2/57	2		75		
IV: 4 HF	M	1952	N																				2/57	5		103		

Family 7

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history										Examinations					
												M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %
III: 1 MA	F	1943	Sv	3	3	3	3	2	3	3t	3	3	0	2t	1	1	1	2	Tooth- erupt 2 Ceph - haem	1	Icr 3	+++	3/57	> 240	4		* under protec- tion of fresh blood.
II: 1 OA	M	1916	Mi	1	1															Icr 2 Fract -		2/59 5/62 57	> 60 > 60 s 1	4 27			
I: 4 HSN	F	1882	Mi	1									1	1	1			P1 2	1		+	57	6*	1	27		* test at lo- cal hosp.
II: 4 EA	F	1920	N										-									57	2		146		

22 Table 2 (continued)

Family 8

Bleeding history																				Examinations								
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 1 RB	M	1926	Sv	3	3	2	3	3	3	3	2	2	1	1	1	1	3/Tooth- erupt 3 t- I.m. I	Fibrome	2	+++	5/42	>60*						* test at lo- cal hosp.
																						4/43	24*					
																						8/52	>30*					
																						3/57	>60			4		
																						3/57		6		10		
																						6/61						
																						11/61						
																						11/68				6		
																									3			
I: 2 EB	F	1899	Mi	1							2	-									+	1	3	13	68		Menopaus	
I: 1 GB	M	1893	N																			11/69	2	3	11	105		
I: 1 AMB	F	1953	N																		-	3/57	1		95			

Family 9

Bleeding history																				Examinations								
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 ES	F	1938	Sv				2	3	t	2	2	0	3	1		1	1	2/I.m. 1	2	Skin t-	73	+++	51	> 30				
																							7/57	>240		2		
																							3/59	> 60		3		
																							10/62			5		
																							1/64			4		
																							1/68	> 30	>30	3	6	
																							57	6		45		
																							57	3		33		
																							10/62	3		56		
																							5/67	1	10	100	52	Menopaus
																							57	1		80		
																							57	4		123		
																							57	3		69		
																							5/67	1	15	85		
																							5/67	1	8	95		
																							57	3				
II: 11 GvS	M	1928	Mi																			—						
II: 7 KS	F	1913	Int.																			—						
I: 4 EvS	F	1890	N																			—						
II: 4 PS	M	1910	N																			—						
II: 8 MB	F	1915	N																			—						
II: 9 BE	F	1918	N																			—						
III: 2 LS	M	1941	N																			—						
III: 3 GS	F	1945	N																			—						

Table 2 (continued) Family 10

Bleeding history																										Examinations			
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 MCA F																													
		1932	Sv	3	1	2	3r	3	0	3r	1	1	1	1	1	1	1	1	P12	2	Curett Plt-	+++	9/55 7/57 7/60 1/62 11/64 5/67 9/67	>30 >60 >60 >30 >30 >30 >30		17*		* pleurisy	
II: 3 KN F																													
		1902	N						0													—	5/67 5/67 5/67 5/67 5/67 68	4 6 1 2 3 2 3	13 75° 10 90° 13 97° 12 65° 9 65 8 102			Menopaus	
II: 8 VS F																													
		1905	N						---													—	5/67	1					
III: 2 GS F																													
		1933	N						-													—	5/67	2					
III: 3 DA F																													
		1940	N						-													—	5/67	3					
III: 4 SGS M																													
		1942	N																			—	5/67	2					
III: 1 VS F																													
		1962	N																			—	68	3					

Family 11

Bleeding history																				Examinations									
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 1 GB M																													
		1913	Sv	1	2	2	3t			3t				1	1	1	1	1	Hpt 2	2	Max 2 Abd t 3 Intest t -	++ +	12/57 4/65 11/65 11/65 12/65 11/66 3/67	40 > 30		10 30 17 19 3 3			

Family 12

Family 12		Bleeding history														Examinations															
		Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
IV: 2 KPA		F	1948	Sv	3r	1	3	3	3	0	1	1	2	1	1	2	1	1	2	1	1	1	1	++	9/49 10/57	>30 >60			3		
																									2/58 2/58 7/58 1/68	7 5 58 42 >60 >60 >20 >20		4 5 5 17			
III: 2 AA		F	1914	Mi	2					1													+		5/68 6/68 10/57 10/57 10/57	5		59 63 30 36			
IV: 3 KP		M	1952	Mi																		-			10/57 10/57 10/57	4					
III: 1 ML		M	1916	(Int.)	1																										

Table 2 (continued)

Family 13

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 SE	M	1935	Sv	3	1		3	2	2t				1	1	1	1		1 m. 1	3	Ear 3	+++	10/57 5/59 10/68	36		8 8		
III: 3 JIE	M	1945	Sv	1	1		3						1					1 cr 3*	1	1	+++	3/59 4/59	11 7	28 120	5 2	31	* fatal
II: 11 EE	F	1910	Mi	2					2		2	----		1					1	1	+	5/59 6/67	4 2		110 85		Menopaus
II: 10 AE	M	1910	N																		—	6/67	3	20 13			
III: 1 DW	F	1933	N									---									—	5/59	0	2	155		
III: 4 LE	F	1947	N																		—	4/59 10/65	2 2		76 74		

Family 14

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 4 LJ	M	1957	Mi	3	1											2			0		++	5/60 6/65 11/66	20 2 2	12 6 2	10 30 20	45 35 0	
I: 1 JJ	M	1881	(Mi)	1																							
II: 3 BJ	M	1911	Mi	2	2									1		1		Oes 2	1	Oes 1	++	46	6*				* test at local hosp.
III: 1 SC	M	1937	Mi	1																Pl 3		9/57 6/65	6 2	6 2	35 29	0	
III: 2 GJ	M	1941	Mi	2		2							1								+	11/66 11/67 12/63	2 3 8	10 39 32	10 33 39	9	
III: 3 GJ	M	1943	Mi	2	1				1					1		1				2	++	5/64 11/66	5 6	28 30	19 28	0	
II: 1 NJ	M	1902	N	1																	-	11/66	1	11	95	29	
II: 2 KAB	M	1909	N																		-	11/66	1	8	132	6	
II: 4 LJ	F	1916	N																		-	5/60	2		100		
II: 5 EJ	M	1913	N	1																	-	11/66	1	4	9	108	71
II: 6 GJ	M	1915	N	1																	-	11/66 7/68	1 1	3 14	50 168	41 48	

Table 2 (continued)

Family 15

Bleeding history																				Examinations								
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 4 KS	M	1934	Mi							2										-	-	++	10/62	1	5		50	
																				-	-		11/62	5	7	35	45	
																							12/62	2	4	37	44	
																							11/66			14	47	52
																						-	11/66	1	2	15		
I: 2 BS	F	1897	N										1	--						-	-	-	11/66	2	2	11	123	60
I: 1 SS	M	1897	N																			-	11/66	2	2	25	125	
II: 1 RL	F	1924	N								1	-	1	-								-	11/69	3	14	117		
																							11/66	1	1	15	73	39
II: 2 TS	M	1928	N																				11/66	1	1	12	98	29
II: 3 GS	M	1931	N																									

Family 16

Bleeding history																				Examinations									
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 AKZ	F	1946	Sv	3	t	3	3			1	3	t	0		2	t	2		2	Fl.o.m. 2t	3	Hy t 3	+++	58	> 60		4		Anti-AHF shown
																				Retro- per 2			6/61	> 60		2			
																							1/64			3			
																							11/64			4			
																							1/67			2			
																							3/60	3	5	55			
																							11/62	6		75			
																							2/63			59			
																							1/67	2	2	16	67		
																										45			
																							1/67	2	2		53	46	
III: 3 ASZ	F	1959	Int.																										
I: 1 PL	M	1895	N																					11/62	6	4		53	135
II: 2 MZ	F	1952	N																					1/67	2		14	85	26

Family 17

Bleeding history

[illegible]

Family 18

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	Examinations		Remarks		
																										AHF %	Sz %			
II: 1 VÁ	F	1924	Mi	2	1						2	3					1				1	To 2 Chol t 3	++	10/58	4	5				
I: 2 AH	F	1898	Int.	2								---									-	Chol -	+	10/58 11/62 5/67	>60 >30 1	11 33 5	24 33 15			Menopaus
II: 3 GH	M	1928	Int.	2								--								1		+	5/67	3	1		8	90°	4	
II: 4 ÁH	M	1931	Int.	2																-		+	5/67	2	2		11	85	26	
I: 1 UH	M	1898	N																			-	11/67	4	5		10	48	18	
II: 2 AH	M	1925	N																			-	5/67	1	1		12	100	20	
II: 5 TH	M	1938	N																	-		-	6/67	3	3		7	95°		
																				-		-	5/67				9	50		
																				-		-	11/67	3			7	45°	61	
III: 1 BÁ	M	1954	N																		Veg. ad-	-	5/67	1	1		6	85	52	
																						-	5/67					65°		

Table 2 (continued)

Family 19

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 SA	F	1937	Mi	2	2	2				1	3	3								3	Abx 3 Curet 3	++	1/57 10/58 5/67 6/70 12/70	7 4 8 2 5 5 24 78 2	4 2 5 5 inf. of 200 ml F I-0	94 37 >30 48 ^c 22	17	before inf.
II: 2 JJ	M	1905	N																	-		-	"	5/67	2 0	10 140 ^c	73	24 hours
II: 3 SJ	F	1908	N																	-		-	"	5/67	2 3	9 130 ^c	67	6 hours
III: 2 AGE	F	1944	N																	-		-	5/67	5 5	11 98	12		
III: 3 KJ	F	1951	N																	-		-	5/67	1 2	13 90 ^c	31		
IV: 1 HA	M	1956	N																	-		-	5/67	4	20 70 ^c	0		

Family 20

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 GP	M	1909	Mi	1	1					3										1		++	10/58 11/68	3 8* 5	46 12 35	59		* large drops
I: 2 SP	F	1845	(Mi)	1																								
II: 1 AP	M	1872	(Mi)	1																								
II: 3 TP	M	1875	(Mi)	1																								
II: 5 PP	M	1879	(Mi)	1	1																							
II: 7 FP	M	1884	(Mi)	1																								
IV: 1 BGP	M	1939	Mi	1						2					1					2	Lipoma 2	++	10/58	4 9*	17			* large drops
IV: 2 KGP	M	1941	Mi	3						2										3		++	11/68 10/58	>25 3 7*	30 18	9		* large drops
III: 2 SP	F	1906	N										--									-	11/68 10/58	2 2	45 70	38		Menopaus

Family 21

Bleeding history																				Examinations										
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks		
III: 3 MÅ	F	1931	Mi									3	1	--	1		1		1		1	App- Hy 12 Curett-	+	8/58 10/58 2/59 6/59	12 11	3 1		75 52 45		
IV: 3 OÅ	M	1953	Mi	2																	-	+	11/67 10/58 5/68	3 1 3	7 4 3		90 38	10		
II: 4 HS	F	1904	Int.	2								2	2	-	1		1			2	App-	+	10/58 6/67	5 1	1 1		67 95			
III: 1 SÅ	M	1926	N																			-	10/58	3	2		83			
III: 2 SS	M	1929	N																			-	11/67	3	5	10	95	0		
IV: 1 IÅ	F	1949	N																			-	10/58	3	2		83			
IV: 2 MÅ	F	1952	N																			-	10/58	3	4		120			

Family 22

Case	Sex	Born	Type	Bleeding history										Sum.	Examinations											
				N	G	TS	TO	T	E	GI	UT	M	Part.		O	EH	P	Tr	J	Misc.	TE	Op.	Date m/year	Duke min.	Ivy min.	AHF %
II: 1 ID	F	1943	Sv	3	1	1	2					2	2	1	1	1	1	2	2	3/59 11/62	26 >60 >60	28 s	15			
																			1/63			39				
																			5/65	5		14 s	61			mens VII
																			10/65	8						
																			2/66	>30						
																			1/67	>30						
																				>30						
I: 2 II	F	1910	Int.	1														1	11/62	11	6 s 12 s	76 84				Menopaus
																			1/63							
I: 1 HI	M	1909	N																1/67	1	3	8	160			
I: 2 CI	M	1947	N																1/67	1	3	12	95			

Table 2 (continued) Family 23

Bleeding history

Bleeding history																										
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Examinations	
																									Ivy min.	AHF %

III: 12 KW	F	1951	Sv	2	1	1	3r					3	0	2	1	1	2	To t-	++	7/59	22	10		22																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																													
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I: 2 AMW	F	1883	(Mi)	1																											
II: 1 JKW	M	1913	(Mi)	1																											
II: 2 SE	F	1916	(Mi)									1									-			7/59	2	2		22			
II: 5 NW	M	1927	Mi	1																											
III: 2 BW	M	1952	(Mi)	1																											
III: 7 BW	M	1953	(Mi)	1																											
II: 15 GW	F	1931	N										--		1									5/67	2	2	23*	100	24		* insignifi- cant bleed- ing
III: 13 PW	M	1951	N																					5/67	1	5	10	65	43		

Family 24

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	Examinations	
																										AHF %	Sz %
Bleeding history																											

III: 1 RA	M	1942	Sv	2	2	2	2		1	1	t-	Nose- Vacc.scar 1	++	9/59	49	18		16	
														2/62	19	>30	>30	38	
														5/67				18	
II: 5 BA	F	1926	N											5/67	1	2	9	105-	10
III: 2 AMA	F	1947	N	2					1	0		+		5/67	5	2	13	105 ^c	

Family 25

Bleeding history

Family 25																										
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Bleeding history						Examinations							
													Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date	Duke	Ivy	AHF
																						m/year	min.	min.	%	%

IV: 1 GL	F	1918	Mi	1									3 -	1						2	Veg.ad - lcr 2	++	9/59	8	7		43					
IV: 2 BW	F	1923	Mi									1	0	1					-	Hy 3	+	9/59	9	4		42						
III: 2 MW	F	1889	(Int.)	1																		1/67	9	5		>30	105					
V: 1 KL	F	1953	N																			5/68	2	3		17	65					
V: 2 KL	F	1958	N																1				4/66	4		5 s	85					
																							4/66				64					
																							4/66				58					
																							4/66	5			7 s	72				

Table 2 (continued)

Family 26

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF % %	Sz % %	Remarks
III: 2 EF	F	1939	Sv	3	2	3	2	3					1/3			1				2		+++	54	> 60*				* test at lo- cal hosp. mens IX
																							9/59 2/65 12/66 12/66 12/67	> 60 11 18 22 > 60 2 2 2 1		17		
II: 4 WH	M	1909	Int.																			-						
III: 4 BR	F	1945	Int.									1								1	App-	+	12/66 12/66 12/66 12/66 12/66 12/66 12/66	1 1 1 1 1 1 1 1 2 3 2 2 1 1		45° 45° 40° 80° 74° 55° 70° 78°	45	pregnant menopaus
II: 8 RH	F	1916	N											1								-						
III: 1 BH	M	1938	N																			-						
III: 3 SH	M	1943	N																			-						
III: 5 ILH	F	1949	N																			-						
IV: 1 PF	M	1965	N																			-						

Family 27

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 4 KR	F	1921	Sv	2	1					1	3	0	3	1	1	1	2		2	Chol r 3		++ +	43	> 50*				* test at lo- cal hosp.
																				Curett 3 Joint r -			45	> 90*	5			
																							11/59	> 60	7			
																							11/59					
																							11/64	> 30	4			
																							9/69					
III: 2 ASS	F	1914	(Sv)	2	2							0															17	dead 1929 of nephritis
III: 3 GG	F	1917	Int.								1									Hy -		-	6/67	11	5	14	95°	
II: 3 RS	M	1892	N																			-	6/67	1	1	9	105°	
II: 9 ES	F	1893	N																			-	6/67	2	1	12		Menopaus
III: 1 AMN	F	1912	N												1							-	6/67	1	1	12	80°	Menopaus
III: 5 NES	M	1926	N																			-	6/67	1	1	13	90°	
III: 6 EMS	F	1931	N																			-	6/67	4	2	76		

Table 2 (continued) Family 28

Bleeding history																			Examinations								
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 4 AS	M	1915	Mi	1	1		3												12	App 1 Chol t- Mam 3 Lymph. node t-	++	11/59 11/59 6/62 6/64	10 6 9 4 >30 4 2 2		23 16 25 21		
II: 1 HO	F	1908	Mi	2						2	--								1	Curet-	+	11/64 11/66 11/66	10 4 3 3 1 1	>30 23 19	27 33 44	26	mens VI
II: 6 UBK	F	1927	Mi							--	--	--							-		-		1 1 1 1	19	90	48	
III: 2 IN	F	1939	Mi	1			3			1	0			1		1			t-	Chol t-.	++	11/68 11/59 11/59 11/59 2/62 2/62 1/65 1/67	15 9 4 4 8 3 2 3	12 12 18	48 26 27 32 125 40 115	67	
III: 3 AS	F	1947	Mi									0									-	11/59 12/59 1/62 11/66	6 3 9 10 2 2 3 7	37 43 9 19	81	0	
II: 3 ML	F	1914	Int.	1						1	--	--		1					-		+	11/66	3 7	19	81	0	
II: 2 AH	F	1912	N									--									-	11/66 11/66	2 1 1 1	19 27*	110 97	14 58	* deep in- cision
II: 5 EP	F	1924	N								0									Ex ut 3	-	11/66 11/68	3 2 5	10 11	107 82	32	
III: 1 SJ	F	1933	N																		-						

Family 29

Family 29

Bleeding history																									Examinations				
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks		
III: 1 ICK	F	1926	Mi	1							3	0		1		1			3	Ear 1 Ear t- Trach t- Ov- Ex.ut-	++	11/60 6/62 7/62 5/63	4 1 5 3 2 2 3 1		22	14	11	64 39 41 48	
																				Curet 1 Skinsrpl t 1									
III: 2 ÅW	F	1936	Int.									1							-		-	11/67	8 9	12	95	0			
III: 4 ÅH	M	1945	Int.	1															-		-	11/67	1 1	5	60	17			
III: 3 BF	F	1940	N																-		-	5/67	3 3	10	90°				

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 AW	M	1951	Mi	2t										1			1					+	3/60 12/60 10/61 9/62 11/66	7 3 6 3 5 9 15		38 70 26		
III: 1 AW	M	1951	(Mi)	3*																		—	3/60 9/62 11/66	2 1 2 3 2 1		63 62 78	0	* fatal
II: 4 EW	F	1931	Int.									--										—			9			
III: 3 PW	M	1956	N																			—			11		0	

Family 31.

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 4 LJ	F	1903	Mi	1						1	1	1	---	1	1		1		Hae- morph 1	-	Chol- Chol t- Haemorrh 3	+	1/60	4	9		27	
III: 2 AJ	M	1927	Mi	1													1		2	To 1		+	12/66	8	3	13	41	14
III: 1 GB	M	1923	N																			-	12/66	1	1	17	38°	37
																							12/66	3	2	7	52°	14
																							6/68	2	3	11	77°	39
III: 3 ME	F	1929	N	2									1-1							Chol-		+	12/66	1	2	14	57°	
																							11/68	4	3	4	95°	

Family 32

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IV: 1 AJ	F	1960	Sv	3	1	2	3			1				1	1				2t	2		+++	6/62 10/62 10/62	>45 >50			17	
III: 2 SN	F	1929	Mi									--							Mis- carr -	-	To- Curett -	-			8 s	58		
III: 3 OA	M	1931	Mi																	-			9/62 9/62	3 4 4* 4*		45	* large drops	
III: 5 MJ	F	1937	Mi									--							Mis- carr -	-	Curett -	-			11 s	49		
III: 6 AA	M	1941	Mi																	-	Chol -		9/62 9/62	7 5 4* 4		54	* large drops	
II: 4 BA	M	1903	Int.																	-		-	9/62 9/62	4* 4		53		
II: 7 CA	F	1902	N									---								-		-	9/62	3		77		
III: 1 SJ	M	1932	N									--										-	9/62 10/62	4 4 7 4		87		
III: 4 GB	F	1935	N																			-				100		

Table 2 (continued)

Family 33

Bleeding history													Examinations														
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 AR	M	1942	Sv	2										1	3	2			3	Tartar	3	+++	10/62	>30	>30	19	
II: 8 SR	F	1897	N																12 t-	Tartar t- Fren.ling	2	-	10/62 5/63 5/67	>30 5 >30 6 5	>30	19 36 10 185°	

Bleeding history													Examinations															
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 SP	F	1914	Mi	1	1				3	1	1			1	1	1			2		++	10/58	1 8*			63	* large drops	
I: 1 KL	M	1857	(Mi)						3*														11/58		12s	45		
II: 1 HF	F	1882	(Mi)						3*														4/60	7 6		35		
III: 2 IL	M	1916	Mi						3*														10/62			78		
IV: 3 IL	F	1944	Mi	2	1				1	2	0			1	1	1			2	Gastr	3	++	2/63 1/67	11 3 2	18s >30	88	9	* fatal
I: 1 KL	M	1857	(Mi)						3*														3/60	1 3		54	* fatal	
II: 1 HF	F	1882	(Mi)						3*					1									3/60	7 4		38	* fatal	
III: 2 IL	M	1916	Mi						3*														5/67	8 15	18	67	0	
IV: 3 IL	F	1944	Mi	2	1				1	2	0			1	1	1			2		+		1/68	9 8	28	63	25	
																							3/68	3 3	>30	60		
																							5/68	6 5	18	75		
III: 3 BL	F	1918	Int.																				12/67	1 1	>30	225°		
IV: 4 RL	M	1946	Int.																				6/62	3		88		
																							5/67	3 5	>30			
III: 4 HL	M	1920	N																				11/67	1	7	95	18	
III: 5 IL	F	1924	N																				11/67	5 5	13	175	24	
IV: 1 LP	M	1951	N																				1/67	1 1	12	47		
IV: 2 BL	M	1941	N																2-		+		4/67	5	5	96		
																							4/67		10	107	36	
																							5/67		13			

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 4 PT	M	1905	Mi	1					3							1				2		++	3/60	4	11	16		Anti-AHF shown	
																				12			4/60	5	3	17			
																				1-			6/60	3	3	8			
																							1/62	6	3	15	12		
																							1/62			>30			
																							11/63	4	4	8			
																							11/64	3		11			
																							6/65			29			
II: 10 DS	F	1915	Mi	1	1				1							1			Mis- carr 1	-	App- Ov- Mam 1	+	12/66	4	3	16	83°	0	Menopaus
III: 7 PT	M	1935	Mi																	-		-	2/62	2	3	17	40		
III: 8 AT	M	1938	Mi	1	1															1-		+	2/62			53			
																							2/61	6*	5*	31-		* large drops	
III: 21 GS	M	1946	Mi	1																1		+	5/61	3	2	31			
III: 22 HS	F	1948	Mi										0									+	12/66	4	5	16	49°	25	
III: 23 SS	F	1949	Mi	1									0									-	12/66	1	2	18	63°	45	
II: 6 SC	F	1908	Int.									1										+	12/66	1	1	20	49°	44	
II: 2 PT	M	1900	N													1						-	6/67	1		>30	125°	Menopaus	
II: 3 NT	M	1902	N																			-	6/67	1	2	5	145°	76	
II: 5 NL	F	1906	N																			-	1/67	1	1	19	85	27	
																						-							
II: 9 TP	F	1914	N																			-	6/67	2	3	11	85°		
III: 6 LT	M	1934	N																			-	3/64	4	4	11	100		
III: 9 ET	F	1941	N																			-	1/64	1	3	11	80		
III: 10 SL	M	1936	N	1	1																To 1	+	11/67	2	2	10	185	38	
III: 24 DS	F	1955	N	1																		-	12/66	1	2	9		30	
Family 36																													
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
Bleeding history																													
Examinations																													

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
IV: 2 IN	F	1948	Sv	3	1								1/3			1	1	1	1	1		++	8/60	55	63	2		
																							6/66			>40 s	2	
																							8/68			5		mens IX * fatal
III: 19 KB	F	1904	(Sv)													1						-	6/67	2	2	8	75°	
III: 3 AN	M	1907	N																			-	8/60	5	3	71		
III: 13 MF	F	1911	N	1																		-	6/67	1	1	9	105°	
																						-	6/67	1	1	8	50°	Menopaus
IV: 1 LN	M	1946	N																			-	6/67	1	1	12	80°	
IV: 3 AM	F	1941	N																			-	6/67	3	2			

Table 2 (continued)

Family 38

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
IV: 4 KS	F	1944	Mi.	3	1							2	0	1	1	1				1	Veg.ad 3 Curett-	++	9/60 1/61 2/61 2/61 1/68 1/68 3/68	>60 14 21 8 15	23 10 29 7 1			26 34 32 62 18 >30 >30																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														

Table 2 (continued) Family 42

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history										Sum.	Date m/year	Duke min.	Examinations			Remarks		
												M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.				Ivy min.	AHF %	Sz %			
IV: 62 PS	M	1958	Mi	2t		2							1									++	10/62 10/62 8/67	8 15 9 8 8/67	21 16 40 34					
I: 1 OA	M	1863	(Mi)	1																										
II: 1 EN	F	1888	(Mi)	1																										
II: 2 GA	F	1891	(Mi)	2																										
II: 4 HN	F	1899	Mi	2	1																									
II: 5 AS	F	1903	Mi	1	1																									
II: 7 IA	M	1906	Mi	1																										
II: 8 NA	M	1908	Mi			3																								
II: 9 SP	F	1912	Mi	1																										
III: 2 IN	M	1913	Mi	2																										
III: 3 MR	F	1917	Mi																											
III: 4 AF	F	1923	Mi																											
III: 6 AGC	F	1921	Mi	1																										
III: 9 OA	M	1926	Mi	1																										
III: 10 KA	M	1928	Mi																											
III: 13 IS	F	1936	Mi																											
III: 19 IH	F	1918	Mi	2	1																									
III: 20 BN	F	1923	Mi	1																										
III: 21 SN	M	1926	Mi	1																										
III: 22 MP	F	1928	Mi																											
III: 24 IN	M	1935	Mi	1																										
III: 25 SN	F	1937	Mi	2	1																									

* test at lo-
cal hosp.
mens III
mens IV
mens III
* test at lo-
cal hosp.
** fatal
* test at lo-
cal hosp.

88 Table 2 (Continued)
Family 42 (continued)

Family 42 (continued)														Bleeding history										Examinations				
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 26 EN	F	1940	Mi	2								1	0		1	1	1					+	5/62 8/67	>30 >30	10 45	>30 45	30 1	
																						+	5/62 1/67	9 2	9 5	>30 >30	43 30	16
III: 27 KZ	F	1930	Mi	1	1							3-			1	1	1					++	9/67 10/62	6 3	>30 3	>30 42	32 12	18
III: 28 KE	F	1939	Mi	1								--										+	8/67 10/62	2 3	>30 29	>30 29	40	
																						+						
III: 31 IS	F	1932	Mi	1	1							2	---									+	11/62	4	3	24	44	
III: 32 NOAM	M	1934	Mi	2												1						+	11/62 8/67	5 >30	4 >30	41 40	10	
																						+	8/67	3	2	24	38	
III: 33 BAA M	M	1937	Mi	2	1										1				Eye 2	2	App-	++	12/61 1/62	4 2	2 28	30 30	45	1
																						+	8/67	21	45	1	mens VI	
III: 35 KS	F	1940	Mi	1								3	---		1	1	1					++	10/61 5/62 8/67	15 1 8	6 35 45	>30 35 45	48 1	
																							10/68			35	7	
III: 37 IBK	F	1934	Mi									2-										+	5/62 8/67	4 21	3 40	30 21	36 40	6
III: 39 JIA	M	1946	Mi																			-	11/62	3	2	>30	44	
																						-	8/67	3	1	16	45	6
III: 40 LA	F	1948	Mi	1	1							1	0									+	5/62 8/67	3 2	1 27	41 41	6	0
III: 42 MP	F	1953	Mi									1	0			1						-	11/62	2	3	>30	55	
																						-	8/67	10	70	39		
IV: 7 JEF	M	1949	Mi	2	1										1							+	5/62 8/67	2 9	8 43	25 43	48 31	
												2	0		1	1	1				++	1/63	>30					
IV: 12 IC	F	1948	Mi	1	1																	+	10/62	2	3	>30	53	
IV: 16 TA	M	1951	Mi																			-	10/62	1	2	>30	37	
IV: 17 LA	F	1952	Mi																			-	10/62	3	3	>30	31	
IV: 18 ChA	F	1956	Mi																			-	11/62	3	3	38	38	
IV: 24 BS	F	1958	Mi																			+	11/62	3	3	21	43	
IV: 31 HIH	M	1940	Mi																			+	11/62	3	3	25	54	
IV: 33 LH	M	1945	Mi																			+	5/62	3	3	25	43	
IV: 34 GH	M	1947	Mi																			-	11/62	3	3	25	43	
IV: 39 JN	M	1959	Mi	2	2										1	2						+	3/63 8/67	>30 4			49	0
																						+	10/62	4		>30	20	9
IV: 44 MZ	M	1958	Mi	1																		+	8/67			28	40	
IV: 45 AZ	F	1961	Mi																			+	8/67			>30	38	
IV: 46 ME	M	1958	Mi																			+	10/62	4		>15	29	

Table 2 (continued) Family 42(continued)

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Examinations				
																									Ivy min.	AHF %	Sz %	Remarks	
IV: 47 HE	M	1961	Mi	2																			++	10/64	4	30			
IV: 60 AA	M	1960	Mi	1			1				2					1					1		+	10/64	2	>30	75	19	
IV: 61 GA	F	1963	Mi	1													1				-		+	8/67		>30	50	4	
IV: 63 BIS	F	1960	Mi	2												1					t-		++	8/67	8	>30	45	0	
IV: 67 AK	M	1955	Mi													1				2	2		+	5/62	4	32			
III: 41 AIA	F	1943	Int.	1								2				1				1	1		+	5/62	3	7	121		
IV: 3 UR	F	1943	Int.										0			1				2	2		+	5/62	2	16	80		
IV: 25 CS	F	1959	Int.																				+	11/62	2	56			
IV: 38 MN	M	1956	Int.																			-	-	11/62	2	1	45		
II: 3 EA	M	1894	N																			-	-	8/67	1	1	12	87	
III: 1 NEN	M	1911	N																			-	-	10/62	1	1	9	82	
III: 5 MA	F	1919	N																			-	-	5/62	1	1	12s	143	
III: 7 IP	F	1923	N							1											-		-	1/63	7	4	9s	112	
III: 8 EA	F	1924	N													1						-	-	1/63	4	3	9s	91	
III: 11 SA	M	1929	N																			-	-	10/62	3	5	17	85	
III: 12 UL	F	1932	N																		1		-	2/63	1	3	75		
III: 14 GS	F	1927	N																			-	-	4/63	3	3	15	82	
III: 15 EA	F	1930	N																			-	-	10/62	2	1	13	71	
III: 16 UH	F	1931	N																			-	-	11/62	2	1	13	68	
III: 17 MA	F	1933	N																			-	-	10/62	1	4	20	126	
III: 18 LA	M	1941	N																			-	-	10/62	3	1	11	73	
III: 23 GR	F	1930	N																			-	-	11/62	4	1	9	86	
III: 29 BK	F	1929	N																			-	-	5/62	4	4	11	92	
III: 30 SEA	M	1931	N																			-	-	11/62	1	2	17	119	
III: 34 NES	M	1937	N	1																		-	-	11/62	2	3	9	64	
III: 36 LA	M	1932	N	1																		-	-	8/67	1	3	10	68	
III: 38 SP	F	1935	N	1																		+	+	4/63	3	4	14	83	
IV: 6 BIF	M	1944	N																			-	-	11/62	3	4	18	104	
IV: 11 EC	F	1945	N																			-	-	5/62	3	3	8	91	
IV: 19 LGÅ	M	1950	N																			-	-	3/66	8		12	139	
IV: 20 KÅ	M	1948	N																			-	-	11/62	2	1	13	75	
IV: 22 ÅKL	F	1950	N																			-	-	10/62	2	2	12	114	
IV: 23 BS	M	1956	N																			-	-	2/63	3	4	10	120	
IV: 32 BH	F	1943	N																			-	-	11/62	1	3	12	63	
IV: 35 RN	F	1950	N																			-	-	11/62	2	2	11	67	
IV: 36 AN	F	1952	N																			-	-	10/62	2	2	19	82	
IV: 40 BP	M	1947	N																			-	-	10/62	2	3	13	81	
IV: 41 GP	M	1950	N																			-	-	10/62	2	2	12	73	
IV: 48 IK	F	1950	N																			-	-	11/62	1	3	11	104	
IV: 51 IA	F	1958	N																			-	-	11/62	3				

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
Bleeding history																												
IV: 53 KS	F	1952	N																			-	11/62	2 2		15	78	
IV: 57 BMA F		1955	N																			-	11/62		12	125	76	
IV: 58 BGA M		1956	N																			-	11/62	2 1				
IV: 59 Cha M		1957	N																			-	8/67		17	105	80	
																						-	11/62	3 3	20	60	92	
																						-	8/67		14	70		
Examinations																												
III: 4 EJ	F	1910	Mi	1	1					1	2	0			1	1	1				2	App + Ov 2	++	12/60	3 6		46	
																							12/60	6 2		48		
																							12/66	1 1	>30	64	36	
II: 2 COL	M	1875 (Mi)																1				-						
III: 2 EL	F	1901 (Mi)								2	1	1	0						2			-	12/66	1 1	16	85	40	
III: 1 TL	M	1899 N																				-						
III: 3 CB	F	1906 N									1								2			+	12/66	3 2	7	87	57	
Bleeding history																												
III: 2 MH	F	1928	Mi	2	1					2	1	-									2 Hy-	++	2/61	23 1			43	
																							2/61	6 8		37		
I: 3 JM	F	1901	N																			-	11/66	1 1	28		17	
II: 1 EG	M	1922	N																			-	11/66	1 1	10	178	26	
II: 5 HAM	M	1939	N																			-	11/66	2 3	12	97	78	
III: 1 CGG	M	1947	N																			-	11/66	2 2	12	50	87	
III: 2 BH	F	1951	N																			-	11/66	2 1	12	66	28	
																						-	11/66	1 2	15	113	0	
Examinations																												
Bleeding history																												
III: 1 RO	M	1947	Sv	1						2					1		1				2	+	2/61	10 >30			19	
																							2/61	>30		28		
																								>30				
																							2/64	>30		17		
																							12/67			30		
II: 5 ISO	F	1927	Int.																			-	2/61	6 1		50		
																							7/68	1 1	12	58	14	
II: 2 VO	M	1922	N	1																		-	7/68	3 4	8	68	28	

Bleeding history

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 RO	M	1947	Sv	1		2						1	1			1				2	++	2/61 2/61	10 > 30 > 30			19 ⁺ 28	
																				1-		2/64 12/67	> 30 > 30	> 30	17		
III: 5 ISO	F	1927	Int.																	1	-		2/61 7/68	6 1 1 1		50 12	
III: 2 VO	M	1922	N	1																	-	7/68	3 4	8	68	28	14

Table 2 (continued) Family 48

Case		Sex	Born	Type	Bleeding history															Examinations									
					N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 BH	F	1960	Sv	1				1	1	1		1				1	3†	2†		1	++	++	1/62 1/63 5/67	> 20 > 30		11			
II: 1 KH	M	1930	N																		—		5/67 5/67	1 1	> 30	20			
II: 2 MG	F	1939	N																				11/67 11/68	1 1	4 1	15 11	90 140		pregnant

Family 49

Bleeding history																				Examinations									
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 3 AO	F	1919	Mi	1						3							2		1cr 1?	1	App- Salp 2	++	3/61	2	4		57		
I: 2 EN	F	1842	(Mi)	1																	Curett - Mam -		9/61				66		
II: 1 KA	F	1873	(Mi)	1																			6/65	4	5	11	50		
II: 3 AA	M	1879	(Mi)	1						2	2												11/66	4	6	21	69		
III: 1 AE	F	1910	Mi	2	2					1							1		1cr ? 3*	1	Mam 2 Curett 1 Gyn -	+	3/61	2	1		70		* fatal
IV: 3 GS	F	1945	Mi																				9/61				52		
																							6/65	2	2		63		
																							11/66	2	2		52		
																						+	11/66	2	3		8	58	
													3										12/67	1	3	11			
																						-	11/66	1	2	7	78	72	
III: 2 HA	M	1913	N																			-	6/65	3	2		75	38	
IV: 2 HE	M	1940	N																			-	6/65	3	2		75	38	
IV: 7 JB	M	1943	N																			-	11/66	2	3		54		

Family 50

Bleeding history																				Examinations								
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 IA	F	1955	Mi	1									0							2	App 2	+	/65 12/67	1	>30	60	11	
I: 2 MA	F	1927	Mi	2	1					3t		3	3 3 2 2	1			1			2t	App 1	++	/65 12/67	7	>30	55	0	
II: 2 GA	F	1958	Mi	1	1												1			0		+	/65 12/67	4	>30	70	0	
II: 3 EA	M	1959	Mi														1			0		+	12/67 12/67	7	>30	75	34	
I: 4 GA	F	1962	(Mi)	1																								

Table 2 (continued)

Family 51

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Bleeding history										Examinations					Remarks		
													Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %			
III: 3 SÁN	M	1946	Mi	3	1			2					1	1				2	Veg.ad-	+++	12/51	> 120*								* test at lo- cal hosp.
																					12/51	9*								
																					2/52	> 60*								
																					4/52	5*								
																					5/61	12 > 20					53			
																					8/61	> 60					49			
																					> 60									
																					10/61	11 11					73			
II: 2 MN	F	1914	Mi					2	1				1				1	Chol - Curett -	+		1/67	4 2	> 30	43			0			* had taken acetyl/sali- cyllic acid
																					1/67	11* 14*	19	80			5			
III: 1 MN	F	1942	Int.	2								0						1		+	1/67	2 4	12	75			18			
III: 2 HEN	M	1944	N														1		.		1/67	3 3	10	65			69			
Family 53.																														
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date	Duke	Examinations			Remarks		
																									Ivy	AHF	Sz			

Family 53

Bleeding history																			Examinations									
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 IW	F	1929	Mi	1								2	22(3)							2	Sect.caes 3 Curett -	++	12/62 5/63 6/63 12/66 11/68	3 3 6 7 4 3 4 4	15 12 >30 44 54	88 58 42 26 14		
II: 3 RÅ	F	1903	(Mi)									1	---						2	2	Gastr -	++	7/63	3 3	13	57		
III: 1 SÅ	M	1926	Mi							3	2						1			1	App -	-	7/63 12/66	4 3 2 5	15 13	60 119		29
III: 3 EJ	F	1939	N																			-	7/63	4 3	78	131		
IV: 1 KW	M	1950	N																			-	6/63	5 5	14	97		
IV: 2 AW	F	1953	N																			-	11/63	7		137		
IV: 3 MW	M	1962	N														1					-	11/68		13	112		

Table 2 (continued) Family 54

Bleeding history																							Examinations					
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 2 PD	F	1954	Mi							2	0							2	Veg.ad 3*	+	+	5/63 1/67	5 5	22 s 27	34 40	3	* Platelets postop. 38,000/mm ³	
I: 3 EF	M	1889	(Mi)	1																								
II: 4 HF	M	1912	(Mi)	1																								
II: 7 MD	F	1920	Mi	1					1	1	1	-						-	App-	+		5/63 9/64 11/64	2 23 s 23 s	8 s 107 110	65 110			
																						1/67	2	5	18	46	0	
II: 10 VP	F	1929	K(Mi)	1																								
II: 11 BF	M	1932	(Mi)	1																		1/67	1	11	45	8		
II: 3 ND	M	1920	N																			11/67	2	0	15	90	11	
																						1/67	2	2	15	85	9	

Family 55

Bleeding history																									Examinations			
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 3 GF	M	1958	Mi				3							1					-		+	+	4/62 7/63 8/63	3 3	30 29	49 35		
I: 3 AK II: 8 LF	M F	1908 1933	(Mi) Int.	1				3											2	Gastr 3*	-		7/63 8/63 10/69	3 2 3	12 9 9	107 52 49		* fatal pregnant pregnant
II: 5 RF III: 1 LF III: 2 AF	M M F	1925 1953 1955	N N N																		-	-	8/33 7/63 7/63	2 2 3	11 18 18	107 107 79		

Family 56

Bleeding history																								Examinations				
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 2 DH	M	1902	Mi	2	2									1		1		Hae- morrh	2		+	+	10/63	6	6	> 30	25	
																							10/63	4	> 30	20		
																							11/63			25		

44 Table 2 (continued)

Family 58

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 9 AF	M	1957	Mi	1		2								1		1			3		+	5/63 9/63 9/63 5/67	>30 7 4 >30 9 5/67		>30 26	35 27	0
II: 1 FA	F	1892	(Mi)	1															1		+	5/67	2 7	>30	45	11	
II: 2 KF	M	1905	Mi	2																	+						
II: 3 EF	M	1908	(Mi)	1																	+						
III: 1 AMG	F	1937	Mi	1		2						3 2							1	To 2	+	12/67	3 3	>22	40	17	
III: 3 POF	M	1941	Mi	2															2		+	12/67	4 2	>30	40	49	
III: 5 KEF	M	1948	Mi	1					1										-		+	5/67	1 2	27	50	3	
III: 6 IF	M	1951	Mi	1												1	1?		-		+	10/63	6 6	>30	49		
III: 8 IF	F	1954	Mi	2	1							0		1					-		+	5/67	7 4	>30	60	8	
II: 4 GF	F	1919	Int.							1	1	1	1	1							+	5/67 9/63	3 4	20	116	8	
III: 4 IW	F	1946	N																		-	5/67	1 1	-11	85	16	
III: 7 GF	F	1952	N																		-	5/67	1 1	12	90	2	

Family 59

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 TA	M	1944	Mi																0	To 3	+	10/63 10/63	5 3 10 18	14 >30	62 43		
I: 1 FN	M	1892	(Mi)																		+						
II: 2 SA	F	1920	Mi	2						2								1	Mis- carr 1	2	+	5/67	4 4	18	68	19	
II: 5 KN	F	1923	Mi																		+						
II: 7 GÖ	F	1933	Mi															1	2		+	5/67	6 1	23	63	0	
III: 4 IA	F	1957	Mi	1														1	2		+	5/67	3 2	14	50	7	
III: 9 EN	F	1959	Mi	1															1		+	5/67	5 1	22	50		
II: 4 RB	F	1922	Int.																2		+	5/67	1 1	9	50		
II: 1 GA	M	1918	N																2		+	5/67	1 1	18	120	17	
III: 3 IWA	F	1955	N	1																	-	12/67 11/67	1 1 4 3	13	140		
III: 5 KB	M	1946	N	1																	-	5/67 9/68	1 0 3 1	8	65 105	77	

Table 2 (continued)

Family 60

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 2 LJ	M	1956	Mi			2								1		1				2		++	9/63	15*		37		* test at local hosp.	
																				-			11/63	>30	>30	35			
II: 10 ES	F	1929	Mi	2	1							3	-		1	1	1			1	Hy 3 Icr 12	++	12/63	5/67	4	>30	35	0	
II: 13 IJ	F	1933	Mi	2								3	--		1					-	Curet - To -	++	11/63	5	5	>30	35		
III: 1 MJ	F	1953	Int.									0										-	6/64	6	5	>30	113		
																							6/64	5	5	>30	65		
III: 3 LS	M	1950	Int.																			-	5/67	1	2	6	50°	13	
I: 4 HJ	M	1929	N													1						-	6/64	1	1	12	120		

Family 61

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 ALK	F	1937	Mi	2								3	-							2	To 2 Hy 3 Curet 1	++	1/63 2/63 10/63	5 4		48 22 s 39		
III: 1 EK	F	1958	Mi	2t											1					-		++	1/67 3/63	2 6		35	0	
II: 2 KP	M	1940	Int.	2				2														++	1/67	1	2	14	90	36
I: 2 MJ	F	1914	N										---									-	1/67	1	1	9	28	
II: 3 BP	M	1944	N																			-	1/67	1	1	10	75	56

5 Table 2 (continued)

Family 63

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 5 GL	M	1880	Mi	1				3						2	1	1		Hpt 1 - I.m. 2t			+	7/65 7/65 7/65 6/67	1 >17 2 22				
II: 1 HL	F	1871	(Mi)	1				3*											2-		-	11/67 5/67 6/68	3 1 2	3 1 2	>30 11 9	55 55 43*	* fatal
II: 6 JL	M	1884	(Mi)									0									-					70	
III: 4 GL	M	1923	Mi																		-						
IV: 1 ACL	F	1942	Int.																		-						
IV: 2 ML	F	1943	Int.									0						1			-	5/67 6/68 6/67	1 2 4	4 1 4	14 7 15*	40* 35* 60	26 pills pills taken salicyl
III: 1 NL	F	1907	N																		-						
III: 2 GL	M	1913	N																		-	5/67 6/67 6/67	2 2 2	3 4 3	11 8 12	70 55 55	33 64 31
III: 3 EL	M	1918	N																		-						
IV: 3 LL	M	1951	N																		-	11/67 11/67	2 2	3 3	13 13	80 80	18
IV: 4 KL	M	1953	N	1																	-	11/67	2	2	11	80	6

Family 64

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 GJ	F	1950	Mi	1					3			0		2		1		Tooth- erupt 1			++	4/63				40	
I: 1 GK	M	1896	(Int.)	1																		9/63 6/67	>30 12	39 s 2	65 38		
I: 2 MJ	F	1911	N							1						1	1			Chol- App- Gyn-	-	6/67	1	1	13	110 ^c	

Table 2 (continued)

Family 65

Family 65

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history						Misc.	TE	Op.	Sum.	Date m/year	Duke		Ivy		Examinations		Remarks
												M	Part.	O	EH	P	Tr						J	min.	min.	min.	AHF %	Sz %	
III: 1 BS	F	1922	Mi	2	1			1		1	3	0		1		1	Mis- carr 1	1	Chol-	++	10/57	34	24		111*			* upper resp. infect	
I: 1 PGÁ	M	1866	(Mi)	1													Coit 1	App- Mam- Curet 1			1/64	9	5	11 s	28				
II: 2 LA	F	1895	Mi																		2/64				39				
II: 3 LR	F	1897	Mi	1	1						1	0		1		2		App- Hy- Mam-		+	5/67	6	6	>30	52°	2			
II: 6 EMÁ	M	1906	(Mi)	1																+	1/67			>30	50	5			
II: 7 AL	F	1911	Mi	1																+	1/67	2	4	25	45	2			
III: 5 LL	M	1942	Mi	2							2	--3						To- App-		+	1/67			>30	43	10			
III: 2 SR	F	1929	N																-	-	5/67	1	1	6	59°				

Family 67

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	

Examinations

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Family 67

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history							Sum.	Date m/year	Duke min.		Ivy min.		Examinations		Remarks	
												M	Part.	O	EH	P	Tr	J			Misc.	TE	Op.	Date m/year	Duke min.	Ivy min.		AHF %
II: 1 AÄ	F	1949	Mi	2							1	0				2	To 3		10/64	4	6	18	52					
																			8/65	7	4	26	55					
																			5/67	2		9	37					
I: 1 RÄ	M	1923	Mi	1						3						1	App- Vertebr 3	+	8/65	5	4	30	105					alcoholic disease
																		+	9/65	4	4	23	87					
																			10/65	2	2	30	52					
I: 2 EÄ	F	1924	N															—	10/64	2	2	11	54					
																			8/65	5	3	14	100					
II: 2 CÄ	M	1957	N															—	8/65	2	2	16	97					

48
Table 2 (continued)

Bleeding history																				Examinations									
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 1 KH	F	1938	Mi	1									- -	1						-	Chol3	++	10/64	12*					* test at lo- cal hosp.
																					Mam 13		11/64	1	8 s	59			
																							11/64	2	13 s	62			
																							11/64		>40 s				
																							11/67	4	4	19	45	65	
III: 2 TH	M	1959	Mi	2																	Hernia -	+	1/67		11	50	17		
2 LM	F	1913	(Int.)								1																		

Family 72

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history										Examinations						
												M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 1 BB	M	1959	Mi	2											1	1							9/64	5	18 s	57		
																		0	Veg.ad-	+			5/67		> 30	53	10	
II: 2 CB	F	1927	Int.							1			1						Gyn-	+			9/64	1		51		
																							10/64			9 s	78	
																							5/67		18	52	21	

Family 73

Bleeding history																	Examinations											
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 5 SE	F	1925	Mi	1							3	--								2	To 1 Hy 3t Ov t - Hy - Thyr 3*	++	8/64 9/64 6/67			43 13s 2l 22s 45		
I: 2 EJ	F	1896	(Mi)	1						2	3								Mis- carr 3					3				
II: 3 SJ	M	1923	Mi	2															Eye 2	2	Nose 2	+	6/67	1	2	17	35°	* fatal(?)
III: 2 POE	M	1957	Mi	1																1	t -	+	6/67 6/67 6/67	4 5 1	>30s >30s 11	38 33 75°		
II: 1 SJ	M	1919	Int.	1											1		2			2		+	6/67	1	1	6	170°	
I: 2 SG	F	1921	N																			-	6/67	1	1	9	117	
I: 4 SE	M	1919	N																			-	6/67	3		4s	138	
I: 1 CGE	M	1952	N																			-	6/67	3				

Table 2 (continued)

Family 74

Bleeding history

Case	Sex	Born	Type	N	G	T	S	O	E	H	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 EB	F	1909	Mi	1	-	2	1	1								2	+	9/64 10/64 12/64 10/68	4	13 s 12 s 16 s 12	67 28 37		Menopaus
																			9	3		37	

Family 75

Bleeding history

Case	Sex	Born	Type	N	G	TS	O	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 BT	M	1928	Mi	1			1						1		1					3	Hernia /- Vertebr 2 Meato /-	+ +	12/64	7	5	16	43	
																							12/64	4	4	16	52	
																							11/66	2	2		48	0
																							11/66	2	3	16	35	
																							5/67				37	42
																							11/66	2	1	13	81	0
																							11/66	1	0	13	59	29
																							11/66	2	2	10	87	35
																							11/66	1	2	8	128	50
																							11/66	3	3	13	73	
E: 2 MT	F	1906	Mi																									

Family 76

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 2 EB	F	1900	Mi	1			3	1	0	1					1		1			2	Hy 2	+	1/63 2/63 5/67	9 10 7 7 4	13s 19	23 27 50	25	
II: 3 KGA	M	1859	(Mi)				3*														Ves.	—	1/67	2 3	11	90	23	* fatal
III: 1 EA	M	1892	N																		stone 3							

77

Bleeding history																	Examinations													
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks		
II: 7 HR	F	1941	Mi	1						3	-	1	1	1							App	-	+	6/63	35*			* test at lo- cal hosp. mens VII		
I: 3 GJ	F	1906	Mi	1								1	---				1				Ear	-	+	12/66	1	3	15	63	17	
II: 6 GJ	F	1939	Mi			1		1			1	0									-	+	11/66	2	2	14	47	32	Menopaus	
I: 2 BJ	M	1890	N						2										Hae-			+	12/66	1	1	6	83	55		
II: 1 ME	F	1920	N							1											To-		-	12/66	1	2	8		0	
II: 2 BS	F	1923	N																		App-		-	6/67	1	1	13	50		
II: 3 KJ	M	1927	N																			-	1/67	2	2	10	145	22		
II: 4 DJ	M	1937	N																			-	12/66	3	3	14	59	6		
II: 5 RJ	M	1938	N																			-	12/66	1	1	10	44	38		
																							7/68	2	3	12	70	45		

7.8

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke				Ivy				Examinations		Remarks		
																								min.		%		min.		%		min.	%		min.	%
II: 1 HA	M	1957	Mi												1			1		2		+	12/64	3	4	32	7									
																							1/65	3	4	22	18									
																							1/65				17									
I: 1 TA	M	1918	Int.	2																1		+	1/65	4	4	13	107									
																							2/65	5	5	13	114									
2 VA	F	1932	N																			-	1/65	2	2	14	139									

Table 2 (continued)

Family 81

Bleeding history																				Examinations							
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 3 NF	F	1902	Mi						1	---	1								1	Chol - App / - Curet - Eye 2	+	2/65	3	4	26	54	Menopaus
II: 6 VS	F	1910	Mi	1					2	--	1							Hae- morph 1	1	Curet -	+	11/66	2	1	21	103	Menopaus
II: 7 ES	F	1913	Mi	1					1	0	1									Chol 3	+	11/66	4	9	>30	67	Menopaus
II: 11 BC	F	1923	Mi						2	---	1					1			2		+	11/66	1	2	25	50	Menopaus
II: 10 AL	M	1921	Int.													1			2		+	11/66	3	1	16	103	Menopaus
II: 4 AN	F	1904	N																		-	11/66	1	2	19	108	Menopaus
II: 8 KL	M	1915	N																		-	11/66	1	1	14	74	Menopaus
II: 9 EL	M	1918	N																		-	11/66	1	2	14	65	Menopaus
III: 2 GF	M	1928	N	1																	+	11/66	1	2	9	103	Menopaus
III: 3 RF	M	1936	N																		+	11/66	1	2	12	60	Menopaus
IV: 1 RM	M	1950	N																		-	11/66	2	2	16	65	Menopaus

Family 82

Bleeding history																							Examinations				
Case	Sex	Born	Type	N	G	TS	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 1 AT	M	1955	Mi						2									Dent. absc 2	t-		+	4/65	3	3	21	37	
I: 2 UT	F	1923	Int.																			4/65	3	3	22	49	
																						4/65	3	3	26	63	
																						4/65	3	4	23	60	
																						5/65	3	4	24	80	

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history										Examinations		
												M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.

III: 1 AMÅ	F	1929	Mi	1	1	1	3	1	1	1	1	1	1	1	1																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																
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Family 88

Bleeding history

Case	Sex	Born	Type	Bleeding history													Examinations							
				N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.

II: 2 IH	F	1916	Mi										0							1	Hy 3t	++	5/65	4	5			47		
																							6/65	3	3	20	37			
																							6/65	3	4	>30	42			
I: 2 BH	F	1887	Int.																				11/66	1	2	13	28			6
II: 1 SE	F	1907	N																				11/66	2	2	22	102	0		Menopaus
II: 3 GB	F	1920	N																				11/66	1	2	7	88	31		
II: 4 IH	F	1922	N																				6/66	3	3	11	110			
																							6/66	2	2	8	100			

Family 89

Bleeding history

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Examinations		
																									Ivy min.	AHF %	Sz %

III: 2 BN	M	1922	Mi	1	1					3					1		1				-	++	9/65	6			16s	28		
																							2/66			14s	50			
																							1/67	4	1	>30	50	25		
I: 1 NW	M	1900	(Mi)	1																			1/67	1	2	25	45	6		
II: 2 HN	F	1887	Mi							3t					1		1				1	Fract 2	++	5/67	2	1	30	48	16	
IV: 1 MN	F	1951	Mi																		-	-	5/67	1	1	29	95			
IV: 2 GN	F	1956	Int.																				5/67	1	1	10	75	8		
III: 1 KN	M	1920	N																				11/67	2	3	10	75			

Table 2 (continued) Family 90

Bleeding history																								Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 ML	M	1965	Sv	3	1	2									2	2	2			0		+++	11/65	>60*				* test at lo- cal hosp.	
I: 2 IJ	F	1905	(Int)		1										1				I.m. 1	-		+	1/66	6	12s	55			
II: 3 IBL	F	1942	Mi	1							1				1								11/65		>45s	2			
																							12/65	26*			3		
																							10/66						
II: 1 UL	M	1945	N	1													1			-		+	1/66		3	4s	107		
II: 2 BJ	M	1935	N	1																		-	3/66			3s	44		
																							9/66		5s	71			
																							4/67			82			
Family 91																													
Bleeding history																								Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 1 MS	F	1945	Mi	1				1			1	1	0		1	1	1		Hpt 1	2	Veg.ad 2 To 2	++	1/66	2	2	15	73		
																							1/66	2	2	21	68		
																							2/66	2	1	17	54		
																							2/66	2	10	24	43		
																							11/67				53		
I: 1 RS	M	1917	(Mi)						2											Gastr 3*		+	6/66	1	2	11	87		* fatal
II: 3 LS	M	1950	Int.	2																			6/66		12	48			
																							6/66		15	90			
I: 2 GS	F	1922	N																			-	6/66	2	1	10	196		
II: 2 LS	F	1947	N																			-	6/66	5	2	14	119		
Family 92																													
Bleeding history																								Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	

Family 93

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Examinations				
																									Ivy min.	AHF %	Sz %	Remarks	
II: 2 LB	M	1937	Mi	1																	2	Dent. absc 2	+	4/66	16	3	16	32	
II: 1 BB	M	1934	Int.																					4/66	2	6	16	32	
																								5/66	4	4	30	28	
																								12/67	5	6	10	55	
																								11/68	2	3	9	80	32
I: 2 MB	F	1913	N																				11/68	1	2	8	88	54	

Family 100

		Bleeding history														Examinations												
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
III: 4 AS	M	1963	Mi				2t										1	1?		2		+	7/66 7/66 8/66 11/68	3 5 11/68	3 5 19	30 27 24	25 21 20	
I: 1 GL	M	1900	(Mi)							3*	1	1				1	1		Mis- carr 1	2		-	7/66	3 3	3 3	16 38		* fatal
II: 2 MS	F	1928	Mi																				7/66 8/66 12/67 12/67	2 1 1 5	2 1 1 6	19 13 20 17	35 42 20 50	
III: 6 JN	M	1966	Mi				1								2	2	2	2t		0		++						Takes "p-pills"
II: 4 CN	F	1943	Int.																			-	8/66 9/66 7/66 9/66 8/66 8/66 12/66	2 1 3 2 4 2 3	8 14 12 14 14 17	50 80 68 110 117 101 78		
II: 1 AS	M	1921	N																			-						
III: 1 PS	M	1955	N																			-						
III: 2 KS	M	1950	N																			-						
III: 3 JS	M	1953	N																			-						
III: 5 MN	F	1963	N																			-						

Takes
"p-pills"

Table 2 (continued)

Family 101

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	Bleeding history										Sum.	Date m/year	Duke min.	Examinations			
												M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.				Ivy min.	AHF %	Sz %	Remarks
II: 1 MO	F	1927	Mi	2						2	1	3	1										6/66	3	24 s 25 20 s 40			
I: 1 HT	M	1899	Mi	2	1																		6/66	4	14 50			
II: 2 BJ	F	1928	Mi		1					1					1	1							11/67	3 1	13 s 55			
II: 3 AMF	F	1933	Mi																				9/66	2				
III: 5 AF	M	1957	Mi												1	1							11/67	3 7				
III: 2 KO	F	1959	Int.																				11/67	1	20 45		0	
I: 2 GT	F	1900	N	1						1													6/66		10 s 49			
III: 1 AO	M	1955	N		1																		11/67	2 2	14 90			
III: 3 AJ	F	1957	N																				6/66		5 s 74			
III: 4 MJ	F	1959	N																				6/66			84		
																							9/66			99		

Family 103

Bleeding history															Examinations														
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
II: 3 AW	F	1959	Sv	2	3	3	2t							1		2			Umbil 1 3 Eye 1 t-			++ +	1/62 11/63 1/64 10/66 10/66 10/66 10/66 10/66 10/66 5/67 10/66				20 5		
I: 1 WW	M	1924	Mi	2																	Gastr t-	+	10/66 1						

Table 2 (continued)

Family 105

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks	
III: 1 IN	F	1924	Mi	2	1						3	--		1	1				Coit 2	To - App -	++	11/67 11/67 2/68	9 5 3	30 24 30	76 49 59	15 4 4			
I: 2 ALE	F	1873	(Mi)							3										-		-	10/68	3	5	20	63 ^a	40	Menopaus
II: 2 GJ	F	1901	Mi	1																		+	10/68	1	1	17	45 ^a	46	
II: 3 TJ	F	1907	Mi	1	1						0									2	App -	+	10/68	1	1	15	174 ^a	29	
II: 1 AJ	M	1892	N							1												-							

Family 107

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 2 MB	F	1935	Mi	2	1					1		---			1					-	Chol3	++	9/66 9/66 10/66	7 5 3	>20 >30 3	45 43 82		
II: 3 MM	F	1944	Int.																			-	3/67 11/68 10/66	3 3 2	>30 >30 >30	45 213 77	0 20	
III: 1 CB	F	1958	Int.												1							-	3/67 3/67 9/67	1 3 4	25 107 11	88		
II: 1 MB ^A	F	1931	N										1-									-	10/66 10/66 3/67	6 8 1	78 77 13	77 70		
III: 2 IB	M	1960	N																			-	10/66	3	13	96		
III: 3 MB	F	1964	N																			-	10/66					

Family 109

Bleeding history

Examinations

Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 2 LA	M	1926	Mi	1	1														1	2		+	5/67 10/67 12/67	12 4 9	28 26 >25	29 39 43		
I: 1 JA	M	1897	Mi																	-	Prost 3	+	12/67	1	1	14 35		5
III: 1 AA	M	1952	Mi	1	1															-		+	12/67	1	1	10 48	0	
III: 2 KA	F	1952	N																			+	12/67	2	1	10 118	46	

Table 2 (continued)

Family 111

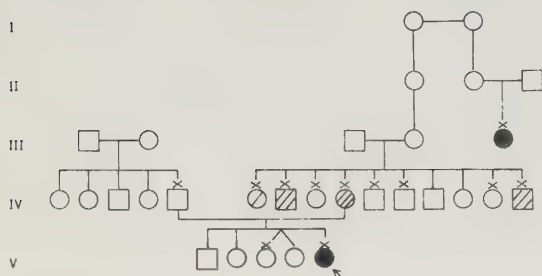
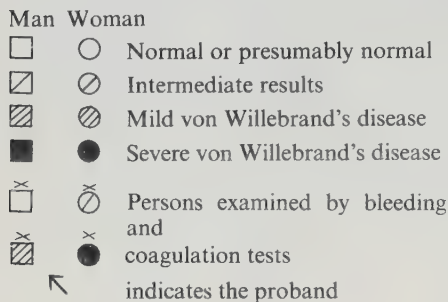
Bleeding history																							Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks
II: 2 TE	M	1962	Mi											1								++	12/67	4	24	24		
																							12/67		20	32		
																							12/67		27	30		
																							1/68		>30	20	30	
I: 2 ABE	F	1938	Mi	2									---								App-	+	1/68	2	>30	44	9	
																							1/68		18			
II: 3 AE	F	1963	Mi																			-	1/68	3	21	35		
II: 1 KE	F	1959	Int.																				1/68	4	10	47		
																							1/68			39		
I: 1 PE	M	1936	N																			-	1/68		8	124		
Family Bj																												
Bleeding history																							Examinations					
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF %	Sz %	Remarks

Family Bj

Bleeding history																									Examinations					Remarks
Case	Sex	Born	Type	N	G	TS	TO	T	E	GI	UT	M	Part.	O	EH	P	Tr	J	Misc.	TE	Op.	Sum.	Date m/year	Duke min.	Ivy min.	AHF % /6	Sz % /6			
II: 1 AB	F	1942	Mi						2	1	1,-	1								-	To-	++	12/67	3	2	19	50'			
I: 1 OB	M	1912	Int.	1																		-	12/67	1	1	16	68	37		
III: 1 AMB	F	1961	N																			-	12/67			10				

CASE REPORTS¹⁾

The following signs were used in the pedigrees:



1 V:5 BT

Gingival bleeding. — At 5–8 years gingival bleeding common, usually round loosening or carious teeth. Hb during concomitant nose-bleeding once fell to 4.8 g/100 ml.

Gastro-intestinal. — At 28 years hospitalised because of haematemesis. Despite blood transfusions and infusions of packed red blood cells and Fraction I-O (F I-O) Hb fell from 7.5 to 4.3 g/100 ml within a few weeks. Treatment was continued and bleeding ceased after about 14 days. The patient had by then received 23 bottles of concentrated red blood cells and 31x100 ml of F I-O. — Subsequent roentgen examination revealed a gastric polyp, which was later removed under protection of F I-O.

Menstruation. — Menarche at 15 years. Menstruation first normal, but later prolonged and profuse. At 15–16 years the patient received all together 82 bottles of blood. The last infusions were followed by severe sensibilisation and hysterectomy was decided upon. (See below!)

Post-extraction haemorrhage. — At 13 years post-extraction haemorrhage. Received 3 bottles of blood. Hb: minimum 9.8 g/100 ml.

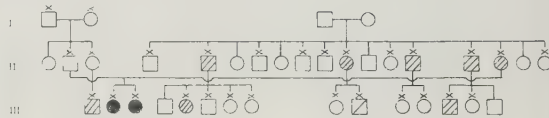
At 18 years extraction of 2 molars under protection of 500 ml F I-O. No abnormal bleeding.

At 23 years tooth extraction twice under protection of fresh plasma, all together 16x400 and 19x400 ml, respectively. No bleeding on first occasion. Fairly profuse bleeding from cavity after —8 for 1–3 days on second occasion. Tooth had had to be divided and levered out. Bleeding stopped after infusion of 100 ml of F I-O.

Hysterectomy. — At 16 years hysterectomy under protection of F I-O: 300 ml before and 400 ml after op. without abnormal loss of blood at or after op. 19 days later bleeding from a small rupture in the vagina after gynaecological examination. Hb fell from 11.2 to 4.8 g/100 ml within 1 hour. The patient was given another dose of F I-O: 200 ml. The bleeding stopped immediately and the rupture was sutured. During the next week the patient received further doses of F I-O, 4x100 ml and the Hb gradually rose to 11 g/100 ml. No blood given during or after op.

Uterine curettage. — At 14–15 years repeated uterine curettage because of menorrhagia but without any effect on the bleeding.

Family 2



2 III:2 YL

Nose-bleeding. — Often had nose-bleeding during childhood. At 14 years, after op. because of ovarian cyst, nose-bleeding, which was cauterised with chromic acid. Blood given on that occasion.

Parturition. — Parturition at 24 years. Towards end of pregnancy (mens VIII) the AHF had risen to 10 % (formerly 3–4 %) while the bleeding time (Duke) had fallen to 22 min. (formerly 60 min.).

After administration of large doses of F I-O: 100+200+300 ml (Fig. 8, page 126), the patient was delivered with vacuum extraction because of secondary weakness of labour. Immediately after parturition heavy loss (about 1,500 ml) of blood per vaginam. The placenta had not separated. The patient went into shock and received 2 bottles of blood, after which the placenta was readily removed. The woman was given methylergotamine (Methergin®, Sandoz) 0.2 g. i.v. and 300 ml F I-O and 500 ml fresh plasma, and the bleeding stopped. Hb fell from 11.8 g/100 ml before parturition to 6.6 g/100 ml the day after parturition.

After parturition the patient received infusions of F I-O (200–100 ml) and fresh plasma (600–800 ml) daily, and the AHF-value then varied between 66 and 170 %. Bleeding time (Duke) was nevertheless sometimes long, about 30 min.

9 days after parturition profuse vaginal bleeding of unknown cause. Injections of Methergin had no effect.

¹⁾ A more complete issue of Case reports is deposited at the Lund University Library and at the Coagulation Laboratory, Allmänna sjukhuset, Malmö.

The patient received 3,500 ml blood within 24 hours as well as all together 600 ml of F I-O. Bleeding afterwards ceased.

The first few days after this heavy bleeding the patient was given F I-O, 200 ml, and fresh plasma, 800 ml a day. Treatment afterwards decreased and gradually withdrawn. The AHF persisted above 50 % as long as the infusions of F I-O were continued, and then fell fairly rapidly to 2–3 % despite some infusions of fresh plasma. The bleeding time was relatively shorter (8 to 22 min.) for several weeks.

No further bleeding.

Ovaries. — At 14 years hospitalised because of a cystic lump, the size of a foetal head, to the right of the uterus, and anaemia Hb 7.4 g/100 ml). The patient received bloodinfusion. At op. (see below) the lump was found to consist of an ovarian cyst. — At 28 years the woman was operated upon for another ovarian cyst (see below).

Trauma. — At 3 years she hit her head against a radiator and sustained an injury about 1 cm long in the occiput. 3 days later severe bleeding from the wound and Hb fell to 5.4 g/100 ml. The wound was sutured and the patient was given a blood infusion of 250 ml, after which the bleeding ceased.

Op- of ovarian cysts. — At 14 years the right ovary and a large ovarian cyst were removed (see above) and appendectomy was done *en passant*. During postoperative course haematoma around op.-wound and prolonged small haemorrhages from granulating areas in op. wound. Further metrorrhagia, nose-bleeding and melæna. Hb fell to 5.3 g/100 ml. The patient received 19 bottles of blood.

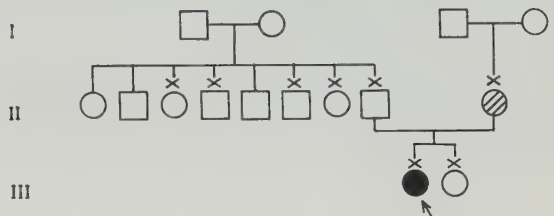
At 28 years left-sided salpingo-oophorectomy for lutein cyst. 800 ml fresh plasma and 200 ml of F I-O given praep. AHF rose to 90 %. Bleeding time not measured. Several adhesions loosened at op. Diffuse bleeding from the raw surfaces stopped by ligatures, continuous sutures and peritonealisation. 500 ml blood infused. Postop. the patient received 200–400 ml of F I–O and 400 ml fresh plasma daily on first 5 days, and then 100 ml of F I-O and 800 ml fresh plasma daily for 6 days. AHF level always above 100 %, bleeding time not measured. Bleeding occurred from abdominal wound and mens-like bleeding from vagina. Hb fell from 12.1 g/100 ml before op. to lowest level of 8.1 g/100 ml 6 days after op. Patient given further 500 ml blood. From 12th day after op. prophylactic treatment of bleeding was reduced and was stopped on 24th day after op. No further bleeding complications occurred.

2 III:3 GL

Menstruation. — Menarche at 12 years. First menstruation profuse with fall of Hb to 10.4 g/100 ml. The patient received 2 bottles of blood and 100 ml F I-O, after which bleeding decreased. During the following 2 years hospitalised on all together 5 occasions because of excessive menstruation. Hb fell to 6–8 g/100 ml, on one occasion to 5.1 g/100 ml. During those years the patient received 13 bottles of blood. On two occasions the patient also received 100 and 200 ml of F I-O.

At 15 years the patient was treated prophylactically with progesterone, 5 mg a day for 10 days before each expected menstruation. The patient improved, but on one occasion she nevertheless had a heavy menstruation, when Hb fell to 8.3 g/100 ml. 3 blood transfusions were given. From 18 years of age she had used "p-pills" and has since not been troubled by menorrhagia.

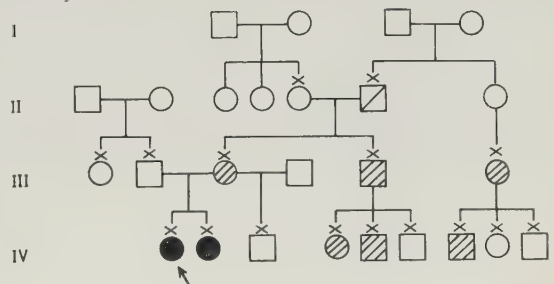
Family 3



3 III:1 MH

Nose-bleeding. — Occasional nose-bleeding between 13 and 17 years. At 18 years after suture of bleeding rupture of the hymen, severe nose-bleeding. The patient received 2 blood infusions.

Family 4



4 IV:1 GB

Gingival bleeding. — At 5–10 years often gingival bleeding, worse after brushing of teeth. Hb on one occasion 9.0 g/100 ml. At 8 and at 10 years gingival bleedings so severe as to require 4 and 5 bottles of blood, respectively.

Menstruation. — After menarche at 14 years profuse menstrual bleeding, which required blood infusions on at least 15 occasions during following years. Roentgen castration at 16 years.

Trauma. — At 7 years stuck a knife through left cheek. Sutured. Bleeding did not stop until after administration of 200 ml blood. Removal of sutures followed by brief bleeding, which stopped spontaneously.

After i.m. injection at 10 years large local haematoma. Hb 6.2 g/100 ml. The patient received 4 bottles of blood.

At 11 years she cut her thumb. Pressure bandage stopped bleeding, which recurred 2 days later on removal of the bandage. Then bled for 24 hours despite pressure bandage.

Joints. — At 7–10 years bleeding in knees and ankles and at 10 years received blood infusions. Right knee became ankylotic.

Intracranial bleeding. — EEG during adolescence showed changes, possibly due to bleeding after fall from horse.

The patient died at 24 years in Greece from intracranial bleeding after trauma against left temple (slap with flat hand). No fracture. Post mortem examination revealed a large haematoma compressing left temporal lobe.

Post-extraction haemorrhage. — At 10–11 years dental treatment at two sittings. Bleeding required 6 and 5 bottles of blood.

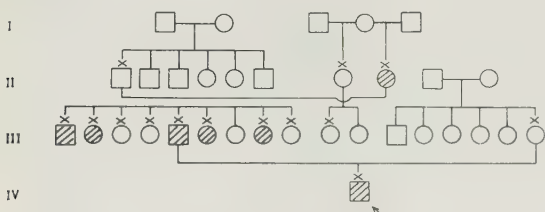
At 17 years dental treatment under protection of F I-O: 500 ml before and 600 ml within 5 days after op. Three days after last infusion she had profuse gingival bleeding with fall of Hb to 5.1 g/100 ml. Received 800 ml blood.

4 IV:2 AB

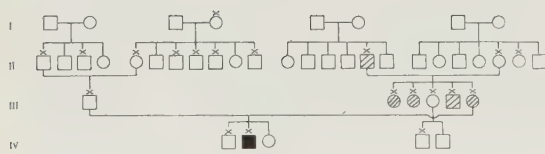
Nose-bleeding. — At 8 years severe nose-bleeding and vomiting of blood during common cold. Patient died from bleeding despite blood infusions.

Joints. — At 4–6 years joint bleedings, particularly in knees and ankles. Right knee ankylosed.

Family 5



Family 6



6 IV:2 RF

Trauma. — Often large soft tissue haematomas after trauma. Cuts followed by profuse bleeding. After a trivial contusion of the neck, when patient was 6 years, Hb fell to 9.0 g/100 ml. At 4 years bleeding from wound of cheek persisted until after infusion of fresh blood.

Prick of fingertip for blood sampling during infancy followed by obstinate bleeding.

After puncture of femoral vein, when patient was 1½ years old, large haematoma in groin and stasis of entire leg. Bleeding ceased after administration of 100 ml F I-O.

Joints. — At 8 years effusion of left knee. Treated with 200 ml F I-O and 3x250 ml fresh plasma. Improved. — At 12–13 years pain and swelling of ankles,

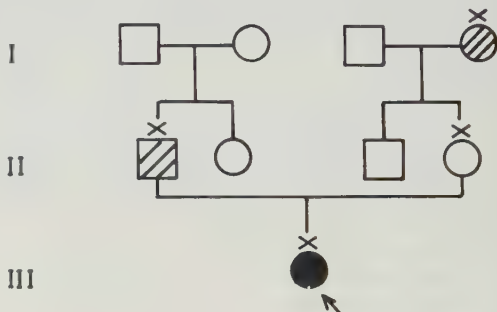
especially left ankle. Better following infusion of fresh plasma. Roentgen examination showed that cartilage in upper part of the joint between talus and naviculae was somewhat thin. — Persistently reduced mobility of left ankle.

Intramuscular and subcutaneous bleeding. — At 12 years tenderness and pain of calf and thigh muscles. Bleeding suspected. 2x100 ml F I-O was given, after which pain ceased.

At 13 years large, fairly superficial swelling of soft tissue in right upper gluteal region. Patient received fresh plasma, all together 1,400 ml. Improved.

Bleeding after puncture of femoral vein: see above under trauma!

Family 7



7 III:1 MA

Traumatic oral bleeding. — At 20 months after a fall obstinate bleeding for more than one week from wound on the underneath side of tongue. Hb fell to 5.6 g/100 ml. Patient received blood infusions.

Urine. — At 5 years dark-red urine during passage of two stones. — At 23 years gross haematuria with passage of blood clots. Hb 12 g/100 ml. Urography: normal. Patient treated first with 2 infusions of fresh blood to staunch bleeding. Improved. At recurrence after a week fresh plasma, 400–600 ml a day, was infused and €-ACA, 5 g.x4, was given for 7 days. Bleeding then ceased and did not recur.

Menstruation. — Menarche at 11 years. During following half year often profuse menstruations. Hb once fell to 4.1 g/100 ml and afterwards often to about 5 g/100 ml. Patient received several blood infusions. Successful treatment for 1 year with progesterone preparation (Progestin®, Pharmacia): 3x5 mg in 2-week periods at end of menstrual cycle. Ergotamine-ergometrinetartrate (Neo-Gynergen®, Sandoz) and adrenon-chloride (Stryphnon®, Chemosan) also given as soon as bleeding started. Menstrual bleeding less profuse also after withdrawal of progesterone.

At 13 years menorrhagia, which was treated with ACTH and cortisone (Fig. 19) but without convincing effect on the menstrual flow.

Intracranial bleeding. — At 3 years subdural bleeding after 2½ m fall from slide. Op. See below.

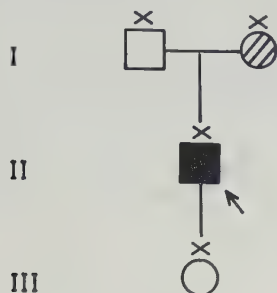
Tooth extraction. — Teeth extracted under protection of blood infusion. No notes about any bleeding.

Intracranial op. — At 3 years subdural bleeding (see above). Op. with removal of dark blood and clots. Some hours afterwards profuse bleeding from op.-region and signs of incipient shock. Blood infusions given. No further bleeding observed but 5 days later Hb was only 7.2 g/100 ml.

II:1 O.A.

Pleural bleeding. — At 53 years after rib fracture pneumothorax and fluid level conceived as bleeding. At op. 2 months later adhesions, which were loosened. No haematoma was found.

Family 8



8 II:1 RB

Haematoma. — Always bruised readily. Hospitalised at 22 years because of large haematoma on posterior thigh without known previous trauma. Hb 11.7 g/100 ml.

Joints. — From 14 months of age often recurrent joint bleeding following trivial trauma or without known preceding trauma, most in knees but also in left hip, left ankle and right elbow. Roentgen showed severe reduction of cartilage in several joints as well as destruction, particularly in distal parts of femur and in both patella. Changes of type seen in haemophilia. Reduced mobility and deformation of several affected joints. Patient walks with a limp. Patient often received infusions i.v. of fresh blood and fresh plasma, 400—1,600 ml, to stop or prevent bleedings. On one occasion he was given 100 ml F I-O. Signs of hepatitis once after plasma infusions (See below).

At 43—44 years used AMCA 0.5 gx2 daily for more than a year. No new joint bleeding during this treatment.

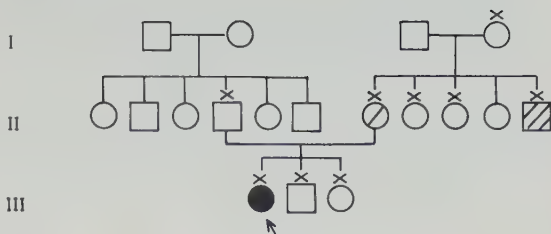
Hepatitis. — At 40 years, some months after infusion of fresh plasma because of joint bleeding, patient showed signs of hepatitis. Bilirubin increase to 18.5 mg/100 ml, GPT max. 558 U, and thymol ext. max. 16 U. One month later much improved.

9 III:1 E.S.

Urine. — At 15 years gross haematuria. Hb fell to 7.5 g/100 ml. Urography revealed nothing remarkable. At 26 years recurrence of haematuria.

Menstruation. — Menarche at 12 years. Menstrual bleedings first profuse, later normal. During the last few years used "p-pills".

Family 9

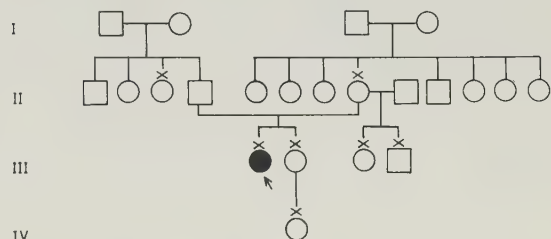


Joints. — Since 7 years of age recurrent joint bleedings in ankles, right knee, right hip, right elbow and, in adult age, also in right wrist. Roentgen examination showed considerable destruction of cartilage and articular surfaces in deformed right elbow and right knee. Range of mobility of the knee and elbow was reduced. Infusion of fresh plasma on various occasions to stop joint bleeding.

Post-extraction haemorrhage. — Oozing post-extraction haemorrhage usually for at least a week.

At 20 years tooth extraction under protection of 450 ml fresh blood and 6x400 ml fresh plasma. Received 2 bottles of blood because of later bleeding.

Family 10



10 III:1 MCA

Gastro-intestinal. — At 18 years bleeding ulcer for which patient received blood infusions on several occasions. At 25 years abdominal pain and melaena. Hb 7.5 g/100 ml. Roentgen examination showed deformation by ulcer but no crater. Received 2 bottles of blood. — At 32, 34 and 36 years melaena. Hb once fell to 6.9 g/100 ml. No roentgen examination. On these occasions blood transfusions were given immediately to replace blood loss, thereafter F I-O was infused: 500, 1,900, and 400 ml, respectively. Bleeding soon ceased during treatment.

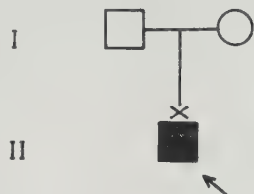
Ovaries. — At 25 and 28 years attacks of abdominal pain and sensation of fullness of small pelvis. Hb fell to 9.1 and 5.1 g/100 ml, respectively. Bleedings from ruptured ovarian cysts were suspected. Treated with blood infusions, on last occasion also with 200 ml F I-O.

During temporary withdrawal of "p-pills" at 35 years patient had similar attacks of intermenstrual pain, and a fist-sized infiltrate was palpated to the right behind the uterus. Treated with 800 ml of F I-O. Also ε-ACA, 4 g.x5, was given for 4 days. Improved.

Pleural bleeding. — At 25 years after bleeding from a ruptured ovarian cyst effusion into left pleura: haemothorax. Treated with pleural puncture under protection of F I-O without abnormal bleeding.

Uterine curettage. — At 19 years uterine curettage because of meno-metrorrhagia. After curettage the bleeding became worse and Hb fell in 4 days from 7.5 to 4.5 g/100 ml. Patient received several bottles of blood. Bleeding did not cease until after injection of ergotamine-ergometrinetartrate (Secatotal®, Astra).

Family 11



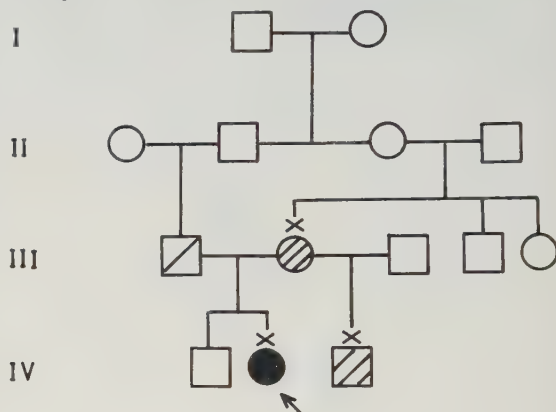
11 II:1 GB

Gastro-intestinal. — At 30 and 31 years gastro-intestinal haemorrhage — given 3 bottles of blood on second occasion. At 44 years melaena twice. Hb once fell to 5.3 g/100 ml. Roentgen examination showed gastro-duodenitis, otherwise nothing remarkable. Patient received 9+14 bottles of blood. — From 51 years of age melaena repeatedly at intervals of 0–3 months. Repeated roentgen examination of oesophagus, stomach and duodenum and colon revealed nothing remarkable. Received numerous infusions of F I-O and packed red blood cells. When given ordinary blood transfusions the patient reacted with fever, which was abated by prednisolone. Also given ϵ -ACA (5 gx4 a day) and later AMCA (1 gx2 — 2gx4 a day), but with only limited effect on the bleedings. Neither did prednisolone in a dose of 30 mg per day produce any effect. Patient granted a sick-pension because of gastric bleeding and continuous anaemia. Finally operated upon to find source of bleeding (see below).

Explorative abdominal op. — In view of the disabling gastrointestinal bleedings of unknown source the patient was subjected to extensive abdominal surgery and vagotomy. The operation was performed under protection of F I-O immediately after a long spell of bleeding from the digestive tract. The patient was in a poor state of nutrition because of narcomania. Serum protein only 4.3 g/100 ml. Praeop. the patient was given F I-O: 300+300+500 ml. The AHF-values reached a high level: over 200% (Fig. 7). Gastroscoy and enteroscopy during op. revealed mucosal haemorrhage. No bleeding was noticed in the op.-field ascribable to surgery. The patient was given 2 bottles of packed red blood cells during op. Intense therapy with F I-O was continued after op.: all together, 1,800 ml on first 2 days and then about 2x200 ml a day. The AHF-level was always above 100%. The bleeding time according to Duke was normal on the day of op. and the first few days afterwards, but on the 5th to

8th day after op. it rose to more than 30 min. despite treatment. During these 4 days the patient bled profusely from the rectum and there was some oozing from the op.-wound. He was given 2,300 ml of packed red blood cells. The dose of F I-O was increased from about 2x200 to 3x200 ml a day. The bleeding time then became normal and the bleeding ceased. Antihæmorrhagic prophylaxis was continued for a month.

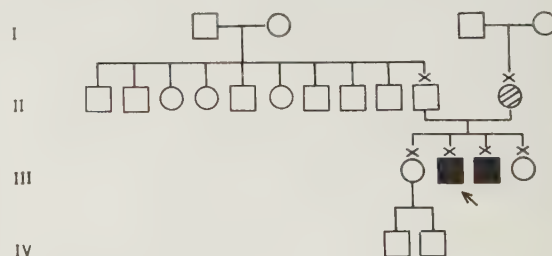
Family 12



12 IV:2 KPA

Menstruation — At 15 years profuse menstrual bleedings, which were controlled with ergotamine-ergometrinetartrate (Secatotal®, Astra). At 19 years very profuse menstrual bleedings with Hb down to 5.2 g/100 ml. The bleedings ceased after treatment with ϵ -ACA and blood transfusions. Gynaecological consultation revealed no local cause of the bleeding. Long-term treatment was started with "p-pills" with good effect on the menstrual bleedings.

Family 13



13 III:2 SE

Nose-bleeding. — Frequent nose-bleeding in childhood, especially during common colds. At 6 years patient had nose-bleeding after op. because of mastoiditis. Hb fell to 4.5 g/100 ml. Blood infusions given. — At 17 years successful treatment for nose-bleeding with AMCA, the bleeding stopped after 6 hours.

Ear. — At 6 years bilateral otitis and anaemia with Hb down to 5.6 g/100 ml.

Urine. — From 14 to 27 years gross, but generally not severe, haematuria, every year or every other year. Urography revealed nothing remarkable. Cystoscopy showed mild bleeding from the bladder neck. On some occasions treated with fresh plasma, at most 7x400 ml with good effect on bleeding. At 34–35 years taken AMCA, 0.5–1 gx2 a day when he had episodes of haematuria and then did not need hospitalisation.

Intramuscular bleeding. — At 33 years "swelling" of left calf after having been run into by a mopedist. Treated with fresh plasma and F I-O. The swelling soon disappeared. About 4 months later signs of hepatitis (see below).

Post-extraction haemorrhage. — At 11 years severe post-extraction haemorrhage. Given 2–3 bottles of blood. — At 22 years tooth extraction under protection of fresh blood, 1 bottle before and 1 immediately after op. Severe bleeding, worst on the 6th day after op. Given all together 31 bottles of blood and 2 infusions of fresh plasma within 1 month.

At 23 years tooth extraction under protection of F I-O, fresh plasma and fresh blood. After 200 ml of F I-O the bleeding time (Duke) was still more than 40 min. AHF 150 %. Tooth extraction was not followed by any bleeding complication. — That year further teeth extracted under protection of 200 ml F I-O before op. and 10 infusions of fresh plasma within 4 days after op. Only mild bleeding at op. 8 days later profuse bleeding from extraction wound. Better after treatment with blood and fresh plasma. During 4 weeks in hospital patient received all together 4 blood infusions and 20 infusions of fresh plasma.

Op. behind the ear. — At 6 years the patient was operated upon because of mastoiditis behind left ear. Profuse bleeding from the op. area for several days. At the same time he had nose-bleeding and bleeding from behind the left tonsil. Hb 2 days after op. 4.8 g/100 ml. Blood infusions given.

Hepatitis. — At 33 years, about 4 months after treatment with fresh plasma and F I-O (see above under intramuscular bleeding) the patient developed signs of hepatitis. Bilirubin increased to 1.5 mg/100 ml. GPT max. 231 U, Thymol ext. max. 4 U.

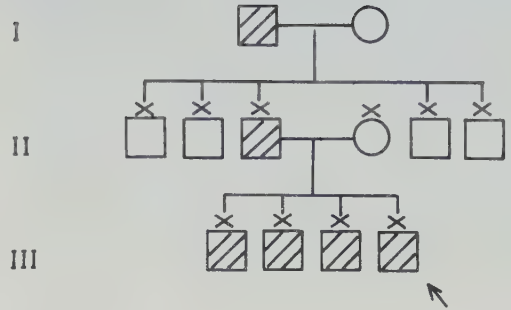
III:3 J.I.E.

Intracranial bleeding. — At 14 years head injury from fall from cycle. He had headache, vomiting and retrograde amnesia. Skull X-ray revealed nothing remarkable. On the first few days after the accident the patient was somewhat cloudy but otherwise in a satisfactory general condition. 6 days after the accident he became increasingly sluggish and after a further 2 days he died. Post mortem examination revealed a haematoma, the size of a hen's egg in the right frontal lobe and small subdural haemorrhages.

14 III:4 LJ

Joints. — At 8 years he fell and hit his right knee, which swelled diffusely and was tender. Immobilisation of the knee in plaster for 10 days.

Family 14

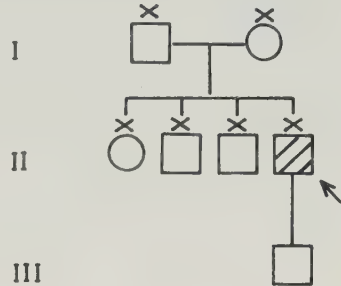


14 II:3 BJ

Oesophageal bleeding. — Cardiospasm. At 35 years coffee-ground vomiting. Hb 10.2 g/100 ml.

Op. on oesophagus. — At 35 years operated upon because of cardiospasm without immediate bleeding. The pleura was opened. First week after op. haemothorax. Repeated pleural puncture produced 600 + 850 + 600 + 300 ml. Received 9 bottles of blood.

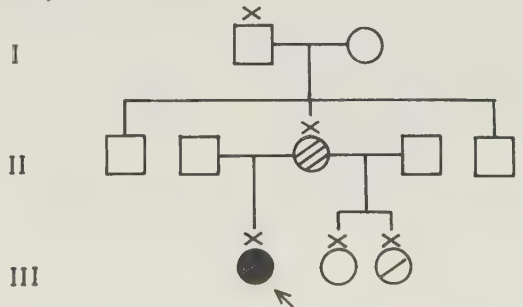
Family 15



15 II:4 KS

Urine. — At 28 years gross haematuria on several occasions. Urography showed on first occasion a cavity in the calyx in the middle part of the left kidney. One week later the change had disappeared.

Family 16



16 III:1 AKZ

Nose-bleeding. — From 3 to 10 years repeatedly hospitalised because of nose-bleeding, received at least 8 bottles of blood. At 15 years troublesome nose-bleeding after hysterectomy; nosebleeding treated with

tamponade. At 16, 17 and 19 years nose-bleeding with Hb down to 8.5 g/100 ml. On one occasion concomitant ovarian bleeding. Patient given blood infusions and on 2 occasions F I-O.

Tooth shedding. — At 8 years given 2 bottles of blood because of bleeding from loosening tooth.

Menstruation. — Menarche at 12 years. First 4 menstrual bleedings very profuse and required repeated infusions of fresh blood and fresh plasma, which, however, did not normalise the bleeding time (Duke). At 3rd menstruation the patient received progesterone, after which bleeding gradually ceased. But during treatment the patient developed haematuria and haemarthrosis. Despite 4 infusions of plasma she also had severe haemorrhage in the floor of the mouth. Fever 40° C. Patient received 5x200 ml F I-O with good effect. AHF-level and bleeding time became normal. The patient soon improved. Progesterone afterwards replaced by methyltestosterone: 5 mg every other day. This kept menstrual bleeding normal, which, however, increased on temporary reduction of the dose of methyl-testosterone. After 3 years' treatment the patient was fairly virilised. Temporary withdrawal of treatment resulted in 2 severe menstrual bleedings requiring treatment with fresh plasma and F I-O. Hysterectomy was therefore decided upon (see below).

Ovaries. — At 16 years (1 year after subtotal hysterectomy) hospitalised twice because of abdominal pain and signs of haematoma in lower part of abdomen. Bleeding in association with discharge of ovum suspected. Simultaneous nose-bleeding. The patient repeatedly received infusions of F I-O, 1,700 ml within 15 days. Treatment with "p-pills" started with good effect on the bleedings. However, during treatment signs of impaired liver function appeared with slightly raised values for GPT, viz. 55–71 U. Treatment with AMCA 1.5 gx2 for 2–3 days was tried at the time of ovulation but the patient developed abdominal pain, which prevented effective continuation of treatment.

Bleeding in floor of mouth. — At 12 years following severe menorrhagia (see above) and numerous blood infusions the patient also bled from the tissues around a carious tooth. The bleeding spread to the floor of mouth and downwards and threatened to obstruct larynx and trachea. The patient then received 5x200 ml F I-O with good effect on the bleeding.

Hysterectomy. — At 15 years, after the patient had been treated for 3 years because of menorrhagia (see above) with testosterone preparation, she had such signs of virilisation that hysterectomy was decided upon. Subtotal hysterectomy was performed under protection of F I-O: 550 ml before and immediately after op. (Fig. 6, page 121). The appendix was removed *en passant*. Loss of blood at op. normal. After op. the patient was given freeze-dried F I-O: 150–200 ml a day for 2 days and the first 4 days after op. were uneventful.

On the 5th day after op. the AHF-value had fallen to 10 %. That day the patient began to bleed profusely through the portio to the vagina. The vagina was evacuated of about half a liter of clots, after which a

tamponade was inserted. But the patient continued to bleed profusely for 5 days despite local tamponades and administration of 300–400 ml F I-O a day. Immediately after infusions AHF increased to over 100 % but then rapidly fell to 21–24 %. Addition of patient's plasma 1/10 to normal plasma caused a slight prolongation of the recalcification time (up to 10 %) as a sign of the presence of circulating anticoagulant. The patient repeatedly received blood infusions. Because of the bleeding cervical cerclage was performed 10 days after op. and during the following weeks the patient improved. Continued treatment with 100–450 ml F I-O a day. 23 days after op. the patient again began to bleed severely from the vagina. The same day she also had nose-bleeding which was successfully treated with tamponon with oxidised cellulose (Oxycel®, Parke & Davis). Vaginal bleeding gradually ceased. F I-O withdrawn. The patient spent 2 months in hospital during which time she received 10,785 ml F I-O as well as 11 bottles of blood, mostly fresh blood. She was sent home in a good general condition.

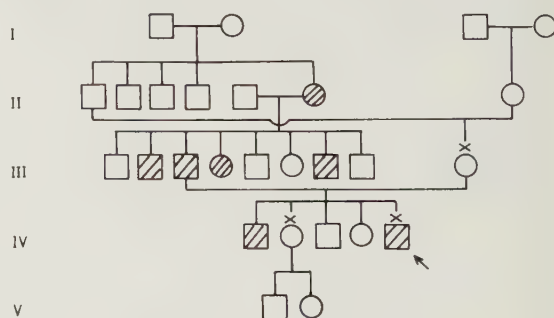
3 months after discharge from hospital the patient developed signs of hepatitis.

Retroperitoneal bleeding. — At 10 years after trauma with consequent effusion in right hip joint the patient also had a lump in the lower part of the abdomen. Roentgenography: psoas-contour diffuse. She developed temporary neurological symptoms: paresis, impairment of sensibility and disturbed reflexes of right leg.

Anticoagulant. — At 19 years examined with refined test for anticoagulant. With the patient's plasma neutralisation obtained of 62 % of AHF in corresponding amount of normal plasma.

Hepatitis. — At 16 years — 4–5 months after she had received intense treatment with blood, plasma and F I-O after hysterectomy — the patient developed signs of hepatitis. GPT max. 2,480 U. Rapid improvement.

Family 17



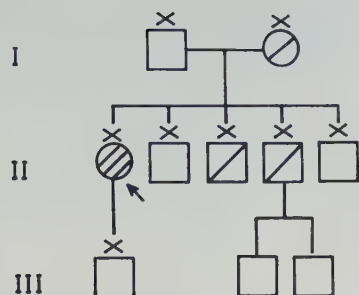
17 II:6 KL

Pulmonary haemorrhage. — Said to have died from pulmonary haemorrhage.

17 III:4 AL

Pulmonary haemorrhage. — Said to have died from pulmonary haemorrhage.

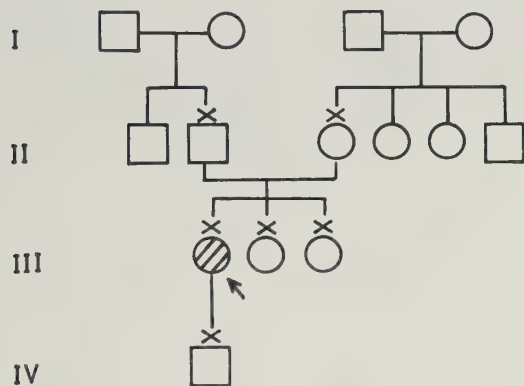
Family 18



18 II:1 VÅ

Cholecystectomy. — At 45 years cholecystectomy under protection of F I-O and fresh plasma. 300 ml of F I-O and 400 ml fresh plasma given before op. AHF value on op. day 77 % and bleeding time according to Duke then 5 min. 20 sec. No abnormal bleeding at op. First 2 days after op. the patient received all together 550 ml of F I-O and 1,200 ml fresh plasma. AHF value 165,50 and 50 %. Bleeding time not measured. Profuse bleeding from wound despite treatment. Given 2x1.000 ml blood and further 600 ml F I-O and 400 ml fresh plasma on 3rd—4th day after op. Op. wound resutured. Bleeding then stopped.

Family 19



19 II:1 SA

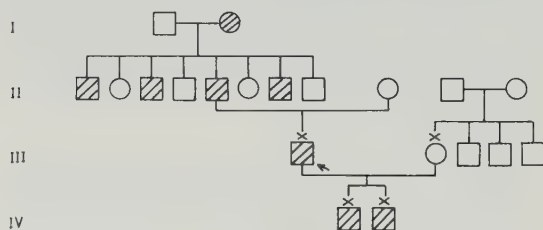
Menstruation. — Menarche at 12 years. The following years the menstrual flow was profuse. At 14 years the patient was hospitalised after uterine curettage (see below) because of menorrhagia and then Hb fell to 3.0 g/100 ml. Given 1 blood transfusion. After parturition at 19 years the menstrual flow was less profuse.

Parturition. — At 19 years. Loss of blood at parturition 800 ml. 4 hours later oozing of blood, which became worse. 15 bottles of blood given within 3 days. Bleeding stopped for one day, then recurred. 2 bottles of blood given. Bleeding stopped for 9 days and then recurred, though not profuse and persisted for several weeks. Patient received 4 further bottles of blood and fibrinogen. Bleeding gradually stopped.

Exaeresis uteri. — At 24 years pregnancy was interrupted in mens II with exaeresis instrumentalis. Patient received 1 bottle of fresh plasma before op. She began to bleed the same day. Moderate bleeding after op. The patient received a further bottle of blood and during the following week all together 8 bottles of fresh plasma. She nevertheless began to bleed again, though mildly, 1 week after op. Hb 10.7 g/100 ml. Bleeding continued for about 1 week and the patient received a further 4 bottles of blood. Hb afterwards 14.7 g/100 ml.

Uterine curettage. — At 14 years uterine curettage because of menorrhagia. After about a day she again began to bleed worse than before and she was admitted to hospital. (See above under Menstruation).

Family 20



20 IV:2 KGP

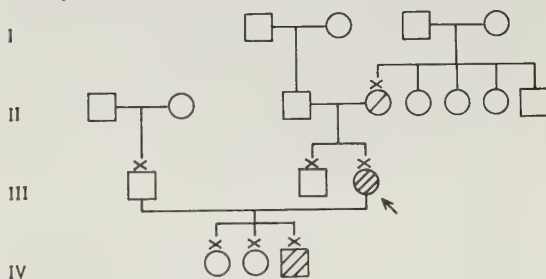
Ear. — At 2 years haematotympanon and concomitant nose-bleeding.

Post-extraction haemorrhage. — At 20 years extraction of +8 without abnormal loss of blood at op. — 3—5 days later increasing bleeding, which ceased after tamponade and suture.

Some months later extraction of +3 under protection of fresh blood: 1 bottle before and 1 bottle after op. Nevertheless bled during postop. course and received a further 2 bottles of fresh blood.

Extraction of -6 at 21 years. Given 1 bottle of fresh blood before and 1 after op. Nevertheless bled again 1 week after op. for which reason a further 2 bottles of fresh blood were given.

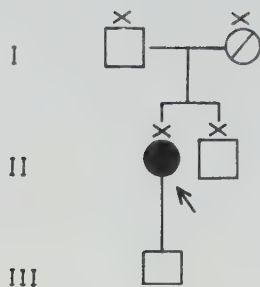
Family 21



21 III:3 MÅ

Menstruation. — Menstrual bleedings always profuse, especially after last parturition, when patient was 22 years. During the following years obstinate anaemia with Hb about 10 g/100 ml. At 27—28 years all together 4 blood infusions. Finally, hysterectomy.

Family 22

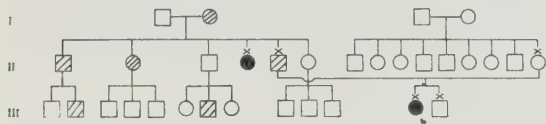


22 II:1 ID

Nose-bleeding. — From 1 to 9 years of age often treated because of nose-bleeding. Hb on one occasion at 1 year 7.2 g/100 ml; at 9 years, 10.9 g/100 ml. — At 25 years a few months after withdrawal of treatment with "p-pills" nose-bleeding with shock. Given all together 10x100 ml F I-O, 10 bottles of blood and 10 of fresh plasma within 9 days.

Menstruation. — Menarche at 12 years. First years very profuse menstrual flow. Admitted to hospital at 12–13 years and at 15 years. Lowest Hb 7.6 g/100 ml. On first occasion the patient received infusions of fresh plasma with good effect.

Family 23



23 III:12 KW

Tonsils. — From 1 to 8 years of age frequent profuse bleeding in association with throat infections, first years the blood appeared to come from the mucosa of the throat, but from 3 years of age it was found to come from inflamed tonsils. At 8 and 10 years life-threatening tonsillar haemorrhages with Hb down to 5.2 g/100 ml. Treated with blood infusions and F I-O: 200 ml each time. — Tonsillectomy finally decided upon (see below).

Tonsillectomy. — At 10 years tonsillectomy under protection of F I-O: 400 ml before and 1,600 ml within 11 days after op. No abnormal bleeding.

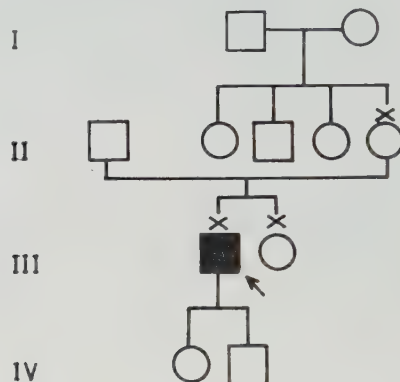
II:4 S.W.

Ovaries. — At 19 years severe abdominal pain during menstruation. Hb 8.3 g/100 ml. Laparotomy revealed a large haematocoele (See below).

Op. of ovarian cyst. — At 19 years operated on because of severe abdominal pain and anaemia (see above under ovaries). Laparotomy revealed around the right ovary a large haematocoele, extending up to umbilical plane. Old clots removed. Salpingo-oophorectomy with peritonealisation. Obstinate oozing of blood from

the wall of the haematocoele, which was very rough. Miculicz duct was inserted as well as a fairly large tamponade. In the later course the patient repeatedly went into shock and despite blood transfusions died 2 days after op. — Also subcutaneous bleeding around op.-wound.

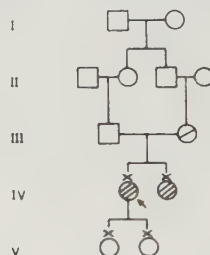
Family 24



24 III:1 RA

Nose-bleeding. — Troublesome nose-bleedings since childhood, especially during physical exertion and after trauma of the nose. At 3 years and 13 years treated with tamponade.

Family 25



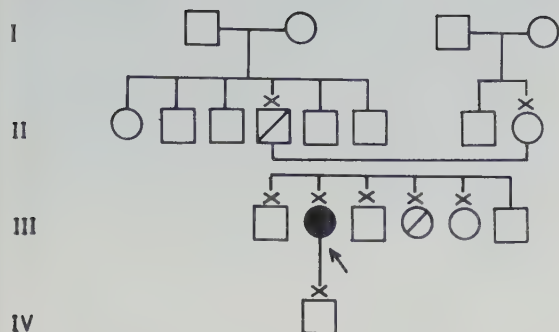
25 IV:1 GL

Op. because of trigeminal neuralgia. — At 41 years op. because of trigeminal neuralgia with division of the root. Local bleeding in op. area and extradurally produced symptoms after half a day and required evacuation on two occasions. Persistent neurological symptoms. viz. double vision and disturbed balance.

26 III:2 EF

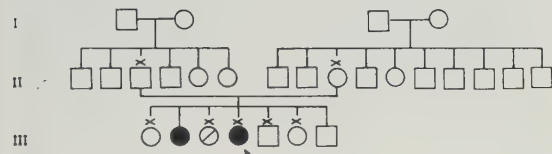
Nose-bleeding. — At 7 months nose-bleeding for 2 days after blow on nose. At 2, 4 and 6 years bleeding from tonsils and nose. The patient received 5 bottles of blood. Admitted to hospital at 15 and 20 years because of nose-bleeding.

Parturition. — Delivery at 26 years. The patient then received 2x100 ml F I-O and on the following days 2 bottles of fresh plasma. No abnormal bleeding at par-



turition or during the first few weeks afterwards. Uterus well involved. 3 weeks after parturition increasing vaginal bleeding. Hb fell from 12.3 to 10.8 g/100 ml. The following week the patient was treated with methylergometrine (Methergin[®], Sandoz), "p-pills" and ϵ -ACA (6 gx4 a day). Furthermore, she received F I-O: 100+100+400 ml, 450 ml fresh plasma and 650 ml fresh blood. But bleeding continued and Hb fell to 8.4 g/100 ml. Finally instrumental evacuation of the uterus with removal of clot and pieces of decidua. Histological examination showed chronic, non-specific endometritis with decidual rests. Bleeding ceased after op.

Family 27



27 III:4 KR

Menstruation. — Menstruation always profuse. Between 15 and 26 years admitted to hospital on all together 10 occasions. Hb once as low as 4.5 g/100 ml. On every occasion the patient received one or more bottles of blood. At 26 years when bleeding had sometimes been life-threatening, roentgen castration.

Ovaries. — On 5 occasions, including 2 at 23 and 24 years, severe abdominal pain and feeling of lump or tension in small pelvis. Symptoms appeared on one occasion after abdominal palpation. The patient once required blood transfusions. These episodes were regarded as symptoms of bleeding from ruptured follicular cysts.

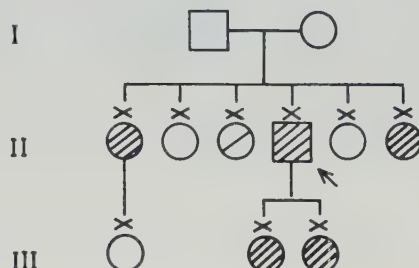
Joints. — Since childhood repeated joint bleeding, mostly in right knee, sometimes also in left ankle and right hip. Impaired range of movement, above all, of right knee. At 43 years range restricted to 170°–80°. X-ray showed considerable reduction of cartilage, uneven joint surfaces and periarticular rarefaction. Changes of the same type as seen in haemophilia.

Cholecystectomy. — At 48 years operated upon with cholecystectomy + choledocholithotomy + drainage. Op. under protection of F I-O, 500 ml before and 5,100

ml during 3 weeks after op. The patient bled diffusely in the op.-field and received one blood transfusion. No abnormal postop. bleeding.

Uterine curettage. — Repeated curettage because of menorrhagia. At 19 years curettage followed by profuse bleeding with Hb down to 3.5 g/100 ml. Several blood transfusions.

Family 28

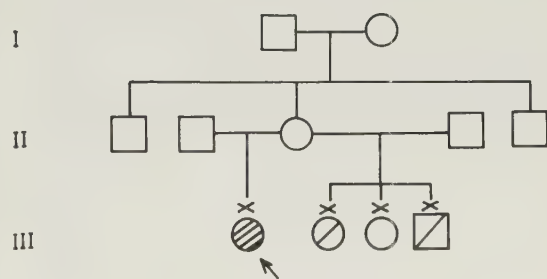


28 II:4 AS

Post-extraction haemorrhage. — At 47 years tooth extraction twice under protection of F I–0: 1,400 and 1,100 ml, respectively (Fig. 15). First extraction of 7 lower teeth, then of 5 upper teeth. On first occasion no abnormal bleeding. On second fairly abundant bleeding, when F I-O had been used from large batches with fresh frozen plasma as a basic material and which had been allowed to stand over night during preparation. Hb fell from 13.6 to 11.2 g/100 ml.

Op. because of gynaecomasty. — At 44 years operated upon because of gynaecomasty. During postop. course blood oozed from op. area. Large haematoma removed the day after op. Hb fell to 10.9 g/100 ml. The patient received 1 bottle of blood.

Family 29

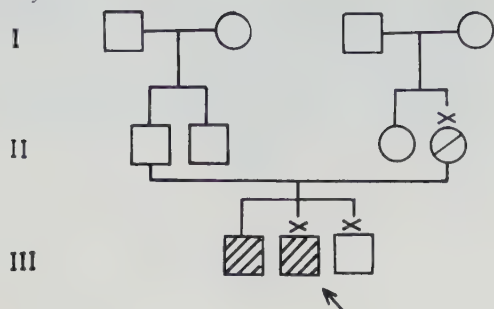


29 III:1 IGK

Op. on ear. — At 34 years operated upon because of otosclerosis. Mild bleeding from auditory duct after op. — Result of op. poor, probably because of bleeding.

At 41 years **stapedectomy** under protection of F I-O, 200 ml before and 200 ml after op. No abnormal bleeding. Hearing improved. Improvement still maintained at control one year later.

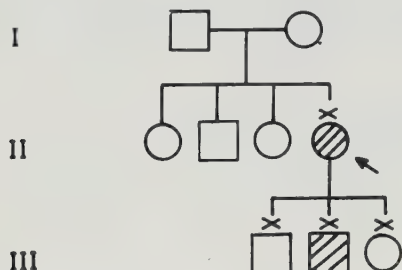
Family 30



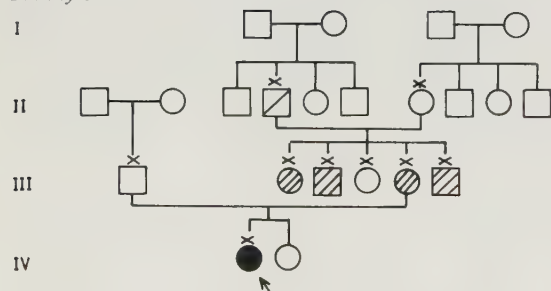
30 III:1 ÅW

Nose-bleeding. — At 7 years nose-bleeding during measles, with shock and death within one day.

Family 31



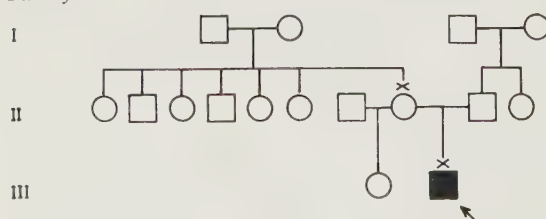
Family 32



32 IV:1 AJ

Haematoma. — Since 4 months of age readily even after trivial trauma. e.g. when she hit the side of the bed.

Family 33



33 III:2 AR

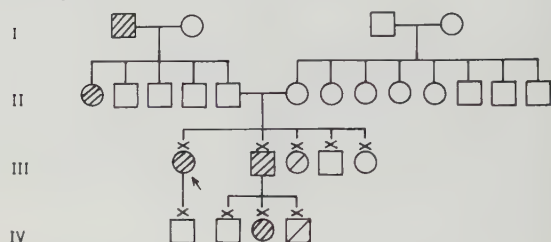
Gingival bleeding. — Tendency to gingival bleeding since childhood, worse once after tooth extraction at 17 years. Sometimes awoke in the morning with mouth full of blood.

Trauma. — After blood sampling from ear at 7 years bleeding persisted until after blood transfusion.

Post-extraction haemorrhage. — Profuse at 17 years. 2 bottles of blood were given.

At 20 and 24 years tooth extraction on 2 occasions under protection of F I-O, all together 1,500 ml and 300 ml, respectively. Last time also given fresh plasma, all together 4,600 ml. On first occasion given F I-O, prepared in a modified way. Rather profuse bleeding, which was, however, controlled by local treatment. On second occasion only little bleeding.

Family 34



34 III:2 IL

Gastro-intestinal. — Occasionally ulcer-like symptoms since 28 years of age and on at least one occasion roentgenologically verified duodenal ulcer. At 40 years operated upon with gastric resection. During following years he had haematemesis and/or melaena on at least 5 occasions. X-ray of stomach and duodenum on those occasions revealed no crater with certainty. Patient often received blood, on one occasion 20 bottles. At 45 years severe gastro-intestinal bleeding and shock. The patient first received blood followed by F I-O, 3x 100 ml within 3 days. No more F I-O available at that time. Bleeding continued and the patient died a few days after onset. Autopsy showed changes suggesting callous gastric ulcer. Autolytic changes made examination difficult.

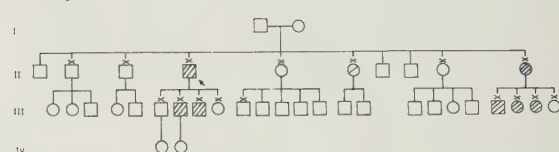
34 I:1 KL

Gastro-intestinal. — Patient said to have died from gastric bleeding.

34 II:1 HE

Gastro-intestinal. — Patient said to have died from gastric bleeding.

Family 35



35 II:4 PT

Post-extraction haemorrhage. — At 55 years severe bleeding after extraction of wisdom tooth.

Later that year extraction of second wisdom tooth under protection of 500 ml F I-O without abnormal bleeding. — At 56 years op. of wedged in 3rd molar and

Family 36

Parturition. — At 20 years delivery under protection of F I - O. (Fig. 9). — AHF in patient's blood 3 weeks before delivery 4.8%. Shortly before delivery the patient received F I - O, 2x200 ml and fresh plasma, all together 1,050 ml. AHF-level rose to 125 %, but bleeding time (Duke) remained prolonged: more than 30 min. Delivery — vacuum extraction after stimulation with Syntocinon drip. On division of shoulders the patient received methylergometrine (Methergin®), Sandoz). On expulsion of placenta fairly abundant bleeding, about 900 ml. After parturition the patient received a further 300 ml of F I - O. During the following weeks given 800 - 1,000 ml fresh plasma a day. Despite treatment and satisfactory AHF-levels: 44-95 %, bleeding time (Duke) was repeatedly prolonged, more than 30 min. and the patient continuously had menstruation-like bleeding. 14 days after parturition, by when AHF had fallen to 12.5 %, bleeding was profuse. The patient received extra doses of fresh plasma, as well as 600 ml of blood and later a further 200 ml of F I - O. Improvement. New episodes with increased bleeding up to 1,000 ml each time 23 and 44 days after parturition. Instrumental evacuation of uterus on both occasions, yield on first occasion interpreted as placental rests. Also on these occasions the patient received extra doses of F I - O: 100-200 ml. From 45th day after parturition the patient was given 100 - 200 ml F I - O a day for 14 days and had no further bleeding.

Joints. — During childhood occasional swelling of the knee, probably joint bleedings.

Menstruation. — Menarche at 14 years. According to hospital records, patient had until then been healthy.

38 IV:4 KS

Family 38

The pedigree chart for Family 38 shows four generations. Generation I consists of an unaffected male and an unaffected female. Generation II consists of an unaffected male and a carrier female. Generation III consists of an unaffected male, a carrier female, and an affected male. Generation IV consists of an unaffected male, a carrier female, and an affected male.

38 III:7 EP

Family 40

The pedigree chart shows three generations (I, II, III). Generation I consists of two couples. The first couple (I-1 and I-2) has six children in Generation II (II-1 to II-6). The second couple (I-3 and I-4) has six children in Generation II (II-7 to II-12). In Generation II, II-5 and II-6 are affected (shaded). II-5 and II-6 have three children in Generation III (III-1 to III-3). III-3 is affected (shaded). The legend indicates that shaded symbols represent affected individuals and symbols with a diagonal line represent carriers.

40 III:3 AMW

Traumatic oral bleeding. — At 1½ years bleeding from lip bite after fall. Admitted to hospital after 2 days, Hb then 10.3 g/100 ml. Continued to bleed, developed signs of shock and was given 2 bottles of fresh blood. At 2 and 4 years prolonged bleeding from small sores on tongue.

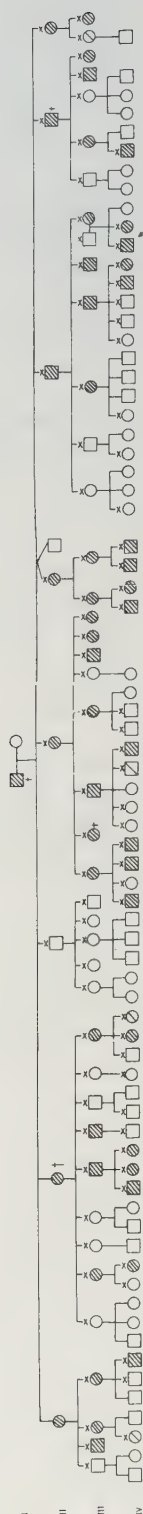
Ear. — Deaf on one side and impaired hearing on other. Not had otitis. Impairment of hearing possibly caused by middle ear bleeding.

Subcutaneous or intramuscular bleeding. — At 8 years admitted to hospital because of fluctuant orange-sized swelling in right gluteal region after fall. Hb 11.3 g/100 ml. Given 100 ml F I-O and 200 ml fresh plasma and the swelling disappeared.

40 I:2 GW

Gastro-intestinal. - Said to have *died* at home from gastric haemorrhage. No autopsy.

Family 41



42 II:2 GÅ

Nose-bleeding and miscarriage. — At 31 years miscarriage with heavy loss of blood. Simultaneous nose-bleeding. Hb fell to less than 10 % according to Sahli (normal 80—100 %) and erythrocytes down to 960.000/mm³.

42 III:19 IH

Parturition. — Bleeding at delivery at 27 years 1,200 ml; at 29 years, 600 ml (patient had on last occasion received oxytocin (Utedrin®), Astra) and secale). Delivery at 23, 25 and 35 years without abnormal bleeding. — During pregnancy at 24 and 35 years, the bleeding time (Duke) became normal in mens IV and mens III, respectively.

Hysterectomy. — At 50 years hysterectomy because of uterine myoma. 400 ml F I-O was given before and 400+100 ml during the first 2 days after op. Patient received simultaneously 9 gx5 of €-ACA a day *i.v.* She bled rather profusely during op., but the bleeding could be stopped by ligation and suturing. The patient received 2 bottles of blood. One week after op. bleeding again began but ceased after re-administration of F I-O, all together 600 ml within a period of 5 days. The patient received a further 2 bottles of blood.

Uterine curettage. — At 50 years uterine curettage+diagnostic biopsy of portio. About one week after op. profuse bleeding, for which the patient received 1 bottle of blood and 200 ml F I-O.

III:20 BN

Pleural puncture and thoracocentesis. — For several years the patient was treated with pneumothorax because of pulmonary tuberculosis. When filling the pneumothorax at 23 and 24 years on a couple of occasions haemothorax. On one occasion after thoracocentesis an orange-sized extrathoracic haematoma. At 24 years the patient was admitted to hospital because of haemoptysis. Thoracocentesis produced thick blood. The patient died the following day.

III:21 S.N.

Nose-bleeding. — After tooth extraction.

III:25 S.N.

Nose-bleeding. — Often in childhood and adolescence, once at 7 years after tooth extraction when the patient fainted. Cauterised, on last occasion at 22 years.

Joints. — At 14 and 17 years haemarthrosis of left and right knee, respectively, after trauma and joint puncture. On latter occasion Hb fell from 11.2 to 7.0 g/100 ml. Patient received blood infusions. No permanent joint deformity.

42 III:27 KZ

Parturition. — After second delivery at 31 years profuse prolonged bleeding from a large vaginal rupture. The rupture was sutured, but the bleeding continued for a week. The patient received 6 bottles of blood.

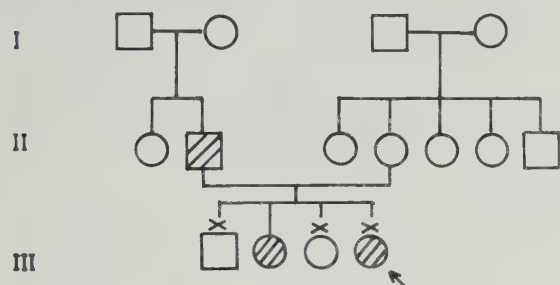
42 III:33 BAA

Eye-bleeding. — At 28 years after trauma troublesome intraocular bleeding, which disappeared within 5 days' treatment with fresh plasma, 400 ml a day.

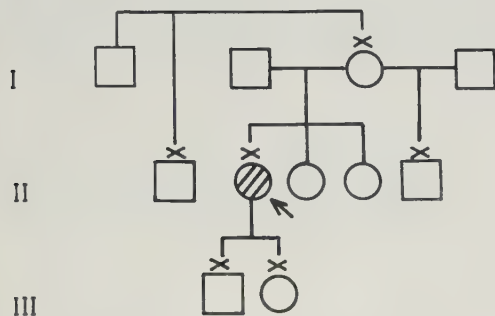
42 III:34 KS

Menstruation. — Menarche at 13 years. Profuse prolonged bleeding at 3rd menstruation, received 2 bottles of blood. Curettage without effect. Bleeding ceased after treatment with chorion-gonadotropin (Pregnyl®, Pharmacia). During the next few years menstrual flow irregular and profuse. Patient admitted to hospital again at 16 years because of menorrhagia, which ceased after curettage. Less copious menstruations after parturition at 18 and 20 years.

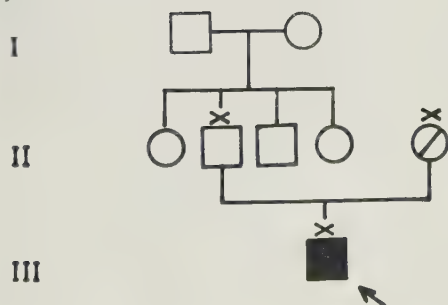
Family 43



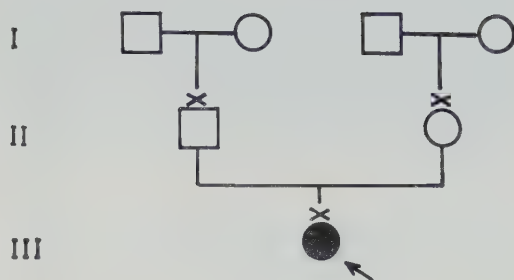
Family 44



Family 45



Family 48



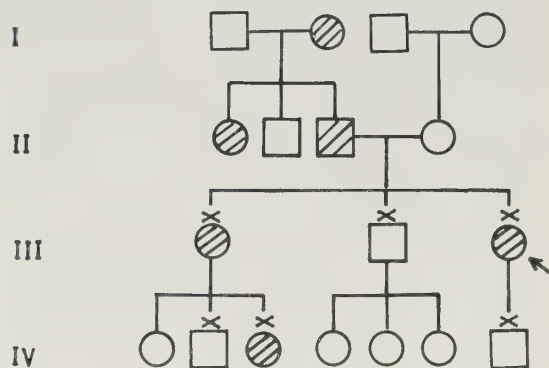
48 III:1 BH

Trauma. — At 7 years hit right knee. Bleeding from wound, which became worse after some hours. Hb that day 8.0 g/100 ml, some days later 6.7 g/100 ml. Patient treated with 2x100 ml F I-O and 200 ml blood after which bleeding ceased.

Joints. — Since 1 year of age trivial trauma caused swelling, pain and impairment of movement of various joints: ankles, knees, elbows and sometimes also wrists. Hb on one occasion during such symptoms 10.0 g/100 ml. Otherwise no anaemia. The symptoms were interpreted as joint bleedings. Range of movement of left elbow permanently reduced. — Roentgen examination showed somewhat deepened joint surface of left elbow, otherwise nothing remarkable. — Treated on some occasions with F I-O: 100–300 ml each time. Once she developed signs of hepatitis 3–4 months later (see below).

Hepatitis. — At 7 years, 3–4 months after infusion of F I-O signs of hepatitis appeared with mild icterus and increase of GOT to 170 U. Soon improved without treatment.

Family 49



49 II:3 AA

Intracranial bleeding. — At 68 years fall from "moderate height" without loss of consciousness. Same day clinical symptoms of cerebral haemorrhage. Examination revealed signs of increased intracranial pressure but not of epi- or subdural bleeding. Death with signs of increasing intracranial pressure. No autopsy.

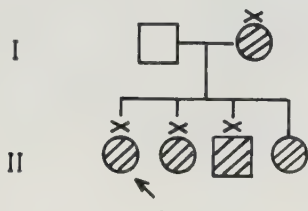
49 III:1 AE

Op. of mammae. — At 49 and 53 years operated upon because of mastopathia cystica. On first occasion no abnormal bleeding. After the second op. a fist-sized haematoma developed in the op. field. Haematoma incised after 3 weeks with removal of large amount of chocolate-brown, thick fluid. Hb had fallen from 12.2 to 10.5 g/100 ml.

49 IV:3 GS

Parturition. — At 22 years parturition. First hours afterwards mild bleeding from vagina, which ceased after removal of placental part. After 1 week recurrent bleeding, which persisted for several weeks. Hb after 3–4 weeks 6.3 g/100 ml. Patient received 2 bottles of blood. Bleeding continued for several months. Anaemia treated with iron medicine. Histological examination of curettings 6 months after parturition: glandular cystic hyperplasia.

Family 50



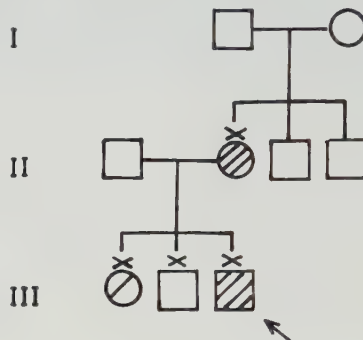
50 I:2 MA

Menstruation. — Menarche at 13 years. Menstrual flow always profuse. Hb at 16 years for several months 6.9–8.5 g/100 ml, at 22 years once 7.2 g/100 ml. On last occasion the patient was given 1 blood transfusion. At 22–24 years regular injection of choriongonadotropin (Pregnyl®, Pharmacia). Menstrual flow became less profuse but since the Hb again fell to 9.1 g/100 ml during menstruation hypophysial implantation was done. No improvement. Patient again admitted to hospital at 26 years because of menorrhagia. Hb then fell to 5.6 g/100 ml and patient was given blood transfusions. At 39 and 40 years menorrhagia and Hb down to 9.0 and 7.3 g/100 ml. On last 2 occasions the patient received 1 blood transfusion each time.

Parturition. — Deliveries at 28, 31, 32 and 34 years. At parturition the patient always bled profusely. After first parturition the patient was given blood transfusion on the second and 6th days. Hb after first transfusion 11.0 g/100 ml, after second 13.1 g/100 ml. 3 weeks after parturition the patient again bled profusely, and bleeding continued for 3 weeks, during which the Hb fell to 10.4 g/100 ml. The patient was given a further blood transfusion after which the bleeding stopped. — After the third parturition the patient was given blood transfusion on the second, 5th and 6th day after parturition. Lowest Hb recorded 8.3 g/100 ml (3 days after first transfusion).

Hepatitis. — After treatment with F I-O because of post-extraction haemorrhage the patient had hepatitis with bilirubin increase to 5.1 mg/100 ml, GPT 2,000 U and Thymol extinction max 0.64 (normal ≤ 0.10). Patient hospitalised for 1 month and when she left hospital the following values were noted: Serum bilirubin 1.7 mg/100 ml, GPT 94 U and Thymol extinction 0.10. She was weak for several months afterwards. Liver function tests gradually became normal.

Family 51



51 III:3 SÅN

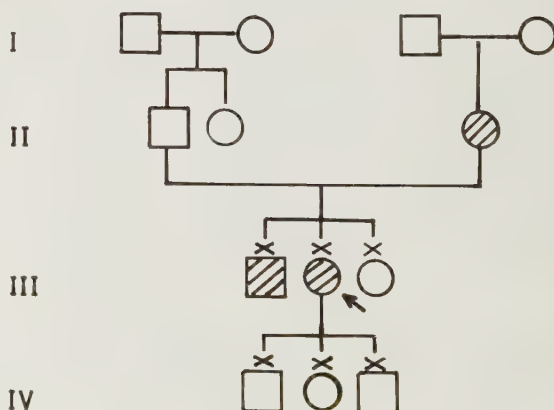
Nose-bleeding. — Frequent nose-bleeding from 2 to 11 years, often requiring hospitalisation. At 10 years Hb fell once to 5.2 g/100 ml. The patient received 5 bottles of blood. At 17 years re-admitted to hospital because of nose-bleeding. Subsequent episodes of nose-bleeding less severe.

Op. veg. ad. — At 6 years curettage of adenoid vegetations. Large adenoid and abundant vegetation removed. Only little bleeding at and after op. Blood values including bleeding time at time of op. said to be normal.

51 II:2 MN

Urine. — At 50–54 years recurrent haematuria. Removal of polyp in bladder neck did not produce desired effect on bleeding. Repeated urography revealed nothing remarkable. Cystoscopy after op. of bladder neck showed nothing abnormal.

Family 53



53 III:2 IW

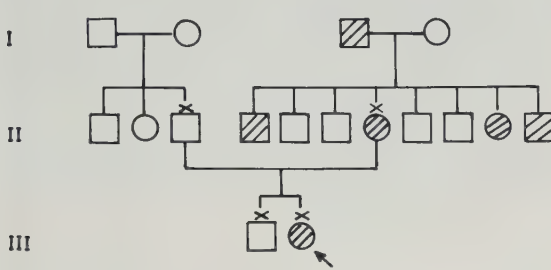
Caesarean section. — At 34 years Caesarean section because of threatened cervical rupture. The first few hours after op. profuse bleeding and shock. No signs of fibrinolysis. The patient received 6 bottles of blood and the following two days 1 bottle on each day. Abnormal bleeding ceased.

53 III:1 SÅ

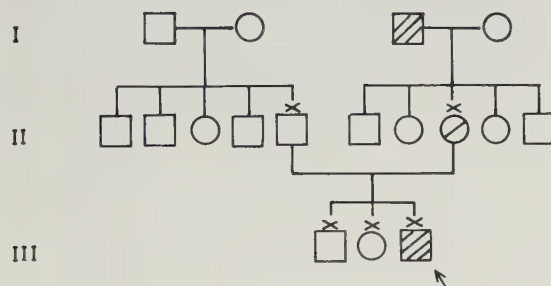
Appendectomy. — At 34 years operated upon because of perforated appendicitis. At op. no abnormal bleeding, but 1 bottle of blood was given. Postop. course uneventful.

Gastrectomy. — At 28 years gastric resection (B. II). One bottle of blood during op. But no notes about bleeding in hospital records. Postop. course uneventful.

Family 54



Family 55



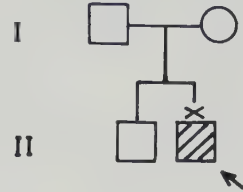
55 I:3 AK

Gastro-intestinal. — At 50 and 52 years severe melaena. Roentgen examination of stomach, duodenum and colon revealed no source of bleeding. Hb on first occasion fell to 5.9 g/100 ml. The patient was given several bottles of blood. At second bleeding episode gastric resection was decided upon.

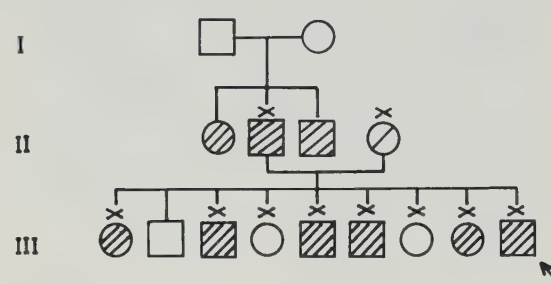
Gastrectomy. — At 52 years, a few weeks after an attack of melaena, the patient was subjected to gastric resection (B.II) because of repeated gastric haemorrhage. At op. a very shallow ulcer about 1 cm in diameter and at least 5 rice-seed sized superficial ulcers were found in the gastric canal. No injured artery to explain patient's severe bleeding. At op. the patient bled readily. Re-suturing was necessary both in the viscera and to the right in the abdominal wall. The day after op. the patient showed signs of intra-abdominal haemorrhage. At laparotomy there was profuse bleed-

ing in op. field but no source of bleeding with certainty. Re-laparotomy 3 days later showed some blood in the abdominal cavity and abundant blood and clots in the stomach. Patient submitted to subtotal gastric resection and the mucosa was found to contain several superficial ulcers. The patient continued to bleed and finally died.

Family 56



Family 58



58 III:9 AF

Post-extraction haemorrhage. — At 6 years profuse bleeding after tooth extraction. Patient admitted to hospital 1 week later with Hb 4.6 g/100 ml. Received 2 bottles of blood.

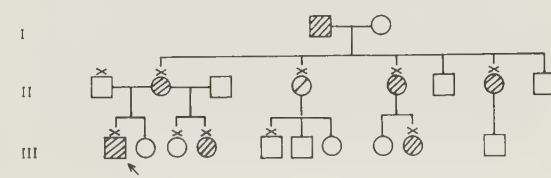
58 II:1 KF

Nose and ear. — Often nose-bleeding since childhood. Cauterised several times. At 58 years left cheek hit by large branch of tree. X-ray showed small fracture in anterior wall of maxillary sinus. Profuse bleeding which ceased after a few hours. One week later severe bleeding from left nostril. Source of bleeding far back in ethmoidal area. Hb fell to 8.6 g/100 ml. — Heamatotympanon bilaterally.

58 III:1 AMG

Tonsillectomy. — Tonsillectomy after 6 days' hospitalisation because of bleeding from tonsils at 14 years. Hb 6 days after op. 9.6 g/100 ml and 11 days after op. 6.1 g/100 ml. Bleeding ceased spontaneously.

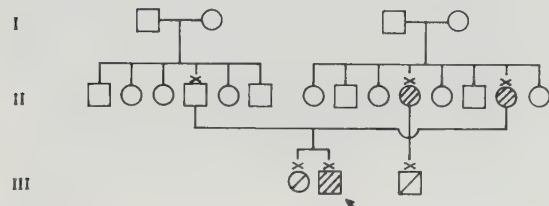
Family 59



59 III:1 TA

Tonsillectomy. — At 19 years severe bleeding on both sides after tonsillectomy. Swelling of surrounding tissue and difficulty in breathing. External carotid artery was ligated and tracheotomy was performed. Profuse bleeding also after these measures. Bleeding continued intermittently one week. Patient given 10 bottles of blood and € -ACA.

Family 60

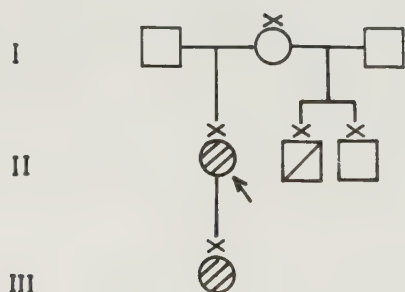


60 II:10 ES

Menstruation. — Since menarche at 14 years always copious menstrual flow. Admitted to hospital at 19 and 20 years, then had Hb 5.9 and 6.4 g/100 ml. Received blood infusions. Better after delivery at 21 years. After second delivery at 23 years symptoms again increased. Troublesome anaemia. At 31 years the patient was tired and weak owing to severe recurrent menorrhagia, and hysterectomy was decided upon (see below).

Hysterectomy. — At 31 years hysterectomy without abnormal bleeding. Patient received 2 bottles of blood. 6 days and 8 days after op. profuse vaginal bleeding. Patient received 2 bottles of blood on one occasion and 4 on the other. No bleeding since.

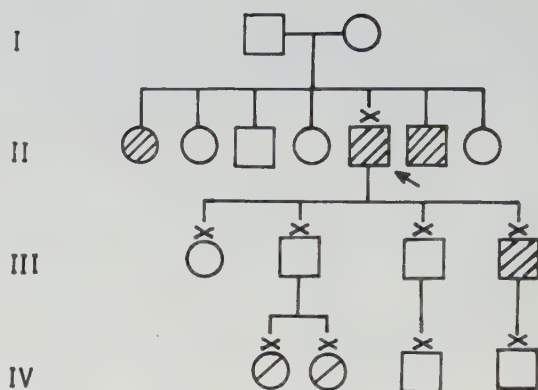
Family 61



61 II:1 ALK

Hysterectomy. — At 26 years hysterectomy because of meno- metrorrhagia. At op. the patient received 400 ml of fresh blood. Op. and the immediate postop. course were uneventful. One week after op. severe vaginal bleeding requiring tamponade and blood infusions. Tamponade was removed after a few days but about 1 week later the patient again began to bleed profusely. She received 1,600 ml blood and was again treated with tamponade. Bleeding then ceased.

Family 63



63 II:5 GL

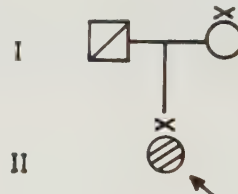
Haemoptysis. — At 85 years haemoptysis and Hb down to 7.8 g/100 ml. X-ray showed changes suggesting bronchiectasis.

Intramuscular and subcutaneous bleeding. — At 86 years pain and swelling of left thigh of unknown cause. Declive haematoma gradually developed. Hb fell to 6.6 g/100 ml. Patient treated with fresh plasma, 10x400 ml and € -ACA. Improved.

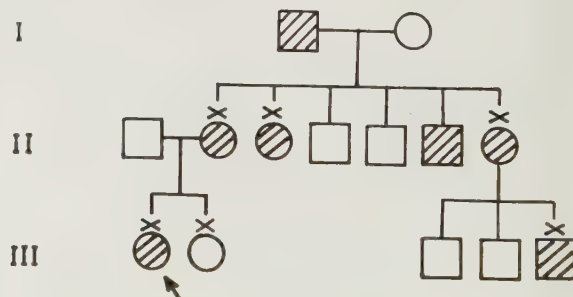
63 II:6 JL

Gastro-intestinal. — Said to have died in America from massive bleeding from duodenum.

Family 64



Family 65



65 III:1 BS

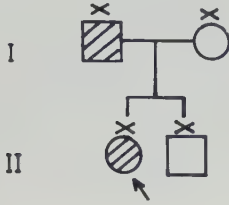
Nose-bleeding. — Frequent nose-bleeding during childhood. Electrocoagulation at least once. — At 37 years admitted to hospital because of fairly severe bleeding after blow against nose. Hb 11.1 g/100 ml.

Ear. — Had spontaneous bleeding.

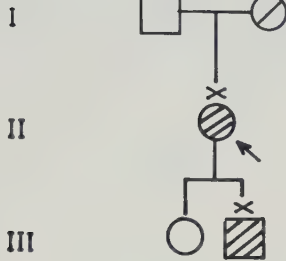
65 II:3 LR

Ablatio mammae. — At 68 years operated upon because of breast cancer. Received 1 bottle of blood at op. Hospital records contained no notes about bleeding at op. Uneventful postop. course.

Family 67



Family 70

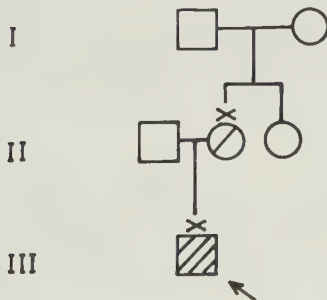


70 II:1 KH

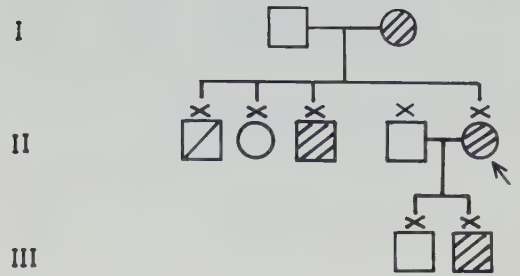
Cholecystectomy. — At 26 years cholecystectomy + appendectomy *en passant*. No notes about bleeding at op. Postop. course uncomplicated except bleeding tendency in wound. Hb, however, fell from 12.9 g/100 ml day after op. to 9.3 g/100 ml 4 days later. Bleeding time (Duke) up to 12 min. Patient received 400 + 800 ml blood, but Hb one month later nevertheless was only 6.6 g/100 ml. Patient received a further 800 + 800 ml blood.

Ablatio mammae. — At 26 years 2 months after cholecystectomy the patient was subjected to ablatio mammae because of nodule in left breast. Op. performed under protection of infusion of fresh plasma on op. day and within 4 days after op.: all together 6x400 ml. Haematoma nevertheless developed in op. field. Hb fell from 12.7 to 9.7 g/100 ml. Patient received 2 bottles of blood.

Family 72



Family 73



73 II:5 SE

Menstruation. — Menarche at 12 years. Profuse menstruations since 14 years. Always anaemic. Hb at 34 years fell on one occasion to 6.0 g/100 ml. Patient treated several times with blood transfusions. After delivery at 27 and 32 years menstruation normal for 18 months, afterwards irregular and of same severity as before. Therefore treated at 38 years with hysterectomy.

Hysterectomy. — At 38 years hysterectomy because of anaemising menorrhagia. Patient bled profusely at op. and received 6 bottles of blood. On 8th—12th day again profuse uterine bleeding. Treated with blood infusions, tamponade of vagina and then resuture of top of vagina. €-ACA, 3 g.x4 given on 11th—15th day after op. Patient improved but €-ACA withdrawn because of suspected pulmonary embolism. Vaginal bleeding recurred and patient continued to bleed for 14 days, and on one occasion fell into shock. She received abundant blood, fresh plasma and later also F I-O. Repeated vaginal tamponade was done and on a further 2 occasions resuture of top of vagina. Last time ligature also round internal iliac artery. After this op. bleeding ceased but recurred after 14 days, *i.e.* 43 days after the first op., but now less severe. Treated then with new ligature + suture and vaginal tamponade. Bleeding then definitively ceased. Received all together 60 bottles of blood, 30 bottles of plasma and 52 1/2 x 100 ml of F I-O.

73 II:3 SJ

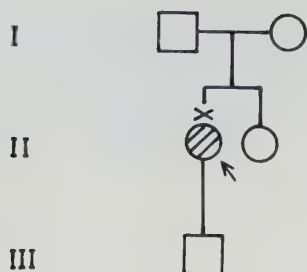
Eye-bleeding. — At 34 years while shooting with an air-gun, splitter damaged left eye. 5 days later severe bleeding behind the eye. Patient became almost blind on that side.

73 I:2 EJ

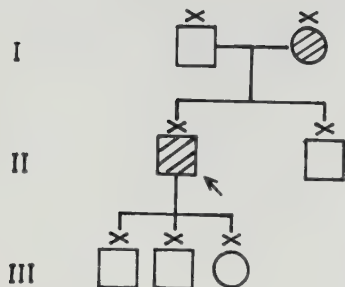
Miscarriage. — At 42 years admitted to hospital because of Uterus myomatosus + Abortus infectiosus mens III—IV + Anaemia gravis. Uterine curettage and instrumental exaeresis. Prolonged bleeding. Hb fell to 6.1 g/100 ml. Patient received 3 bottles of blood.

Strumectomy. — At 55 years operated upon because of non toxic struma. No abnormal bleeding at op. About 12 hours after op. the patient was found dead. Postmortem examination revealed profuse bleeding in op. area and outside anterior part of trachea a large haematoma with two fist-sized blood clots. But these clots said not to have compressed the trachea. — No other cause of death was demonstrable.

Family 74



Family 75



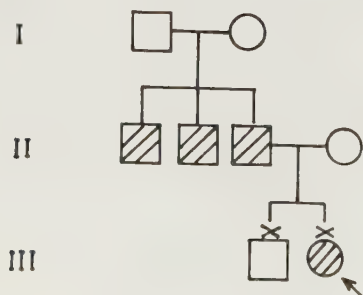
75 II:1 BT

Post-extraction haemorrhage. — After tooth extractions at 21 and 26 years prolonged profuse bleeding, controlled by ligation. — Before tooth extraction at 29 years the patient received 1 bottle of blood. After extraction fairly abundant bleeding for 12 hours. Four days later bleeding recurred and the patient received a further bottle of blood. Hb afterwards 15.4 g/100 ml.

Op. intervertebral disk. — At 28 years operated upon because of herniation of intervertebral disk. Only insignificant bleeding at op. but during following days large haematoma infiltration in entire lumbar region.

Meatotomy. — At 42 years operated upon because of hypospadias with meatotomy under protection of fresh plasma, 600 ml before and 3x400 ml within 4 days after op. No abnormal bleeding. *Eye-lid oedema and hoarseness following infusion of plasma.* Symptoms soon disappeared.

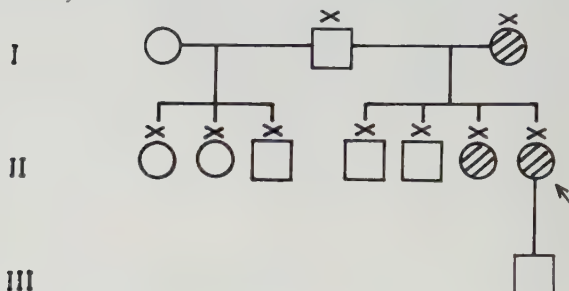
Family 76



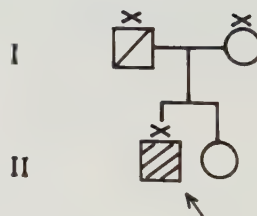
76 II:3 KGA

Gastro-intestinal. — Patient died from gastric bleeding at 46 years. The records confirmed the cause of death but did not mention any bleeding tendency or cause of bleeding. — Two brothers are said to have died from haemorrhagic disease.

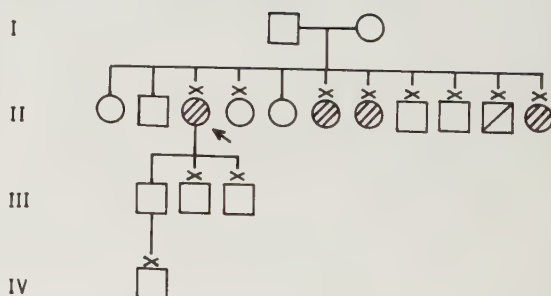
Family 77



Family 78



Family 81



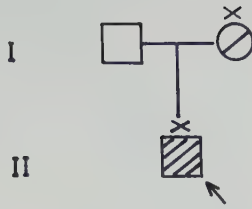
81 II:3 NF

Dacryorhinostomy. — At 52 years dacryorhinostomy with severe bleeding from bed of wound but no gaping vessel demonstrable. Repeated tamponade with adrenochrom (Sangostan®, Difer) and bleeding finally ceased. Hb postop. 15.0 g/100 ml.

81 II:7 ES

Cholecystectomy. — At 49 years. Fairly profuse bleeding during op. from gallbladder bed. Patient received 1 bottle of blood. Smooth postop. course. Hb before op. 13.1 g/100 ml, after op. + blood transfusion 15.5 g/100 ml.

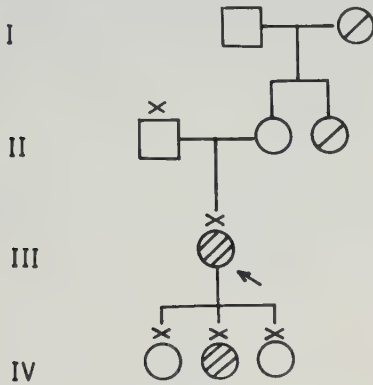
Family 82



82 II:1 AT

Urine. — At 10 years repeated haematuria, particularly in association with physical exertion. Examination at hospital revealed Hb 13.1 g/100 ml and urographic examination showed nothing remarkable.

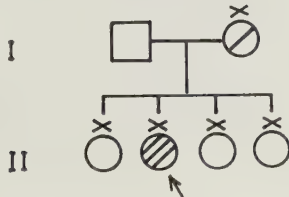
Family 86



86 II:1 AMÅ

Gastro-intestinal. — At 35 years last 10 hours before 3rd parturition, severe haematemesis. Hb fell to 7.5 g/100 ml. Vomiting of blood continued after parturition. Patient received 9 bottles of blood within 1 day. Bleeding ceased. No signs of fibrinolysis. Roentgen examination of oesophagus and stomach revealed nothing remarkable.

Family 88

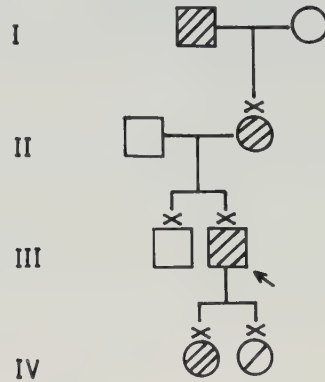


88 II:2 IH

Hysterectomy. — At 49 years hysterectomy because of myoma. At op. no abnormal bleeding. The day after op. Hb 12.6 g/100 ml. During the following days profuse bleeding per vaginam and development of a fist-sized infiltrate behind cervix. Hb 5 days after op. 7.7 g/

100 ml. Patient received 1 bottle of blood and treatment was started with ϵ -ACA, 4.5 gx5 a day. Patient improved, but bleeding did not cease completely. 30 days after op. severe bleeding per vaginam recurred, and Hb fell to 7.4 g/100 ml. Two bottles of blood were given besides ϵ -ACA, 5gx4 for 14 days. But patient continued to bleed profusely for a few weeks and received a further 9 bottles of blood and 4x500 ml fresh plasma and finally 200 ml F I-O (after von Willebrand's disease had been diagnosed). The bleedings then stopped but the patient received fresh plasma also during the following 2 weeks: 5x500 ml. The patient was discharged in a good condition 11 days after the last infusion of plasma and 60 days after op.

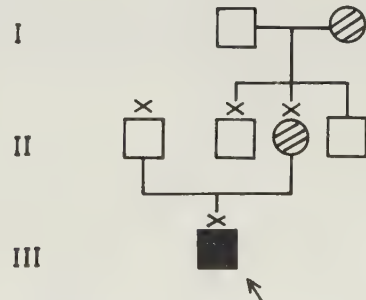
Family 89



89 II:2 HN

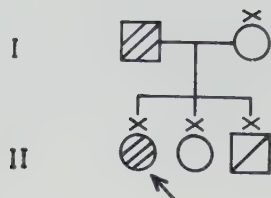
Hepatitis. — Treated for gastro-intestinal bleeding at 81 years with blood, fresh plasma and F I-O. Said to have had hepatitis some months later. No further information obtained, but patient recovered without complications.

Family 90



90 III:1 ML

Bleeding after triple vaccination. — After first triple vaccination at 5 months bleeding for several hours from needle track.



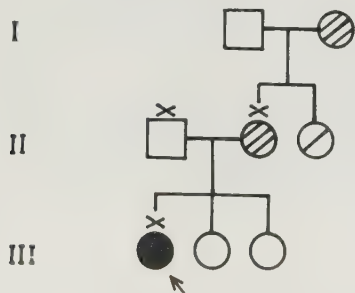
91 I:1 RS

Gastro-intestinal. — Since 30 years of age gastric symptoms, worst every autumn. At 30, 31 and 35 years melaena. On 2 occasions roentgen examination showed severe catarrh but no ulcer, on 1 occasion deformation of the bulb with callous changes, but no ulcer.

Gastrectomy. — At 35 years gastrectomy because of repeated gastric bleeding. No bleeding, however, last weeks before op. Op. revealed widespread extensive perigastritis of the canal and bulb and a small callous wound in the anterior upper margin of the bulbus near the pylorus.

No abnormal bleeding at op. Eight days after op. very profuse bleeding, which continued the following day. Despite several blood transfusions the patient *died*. At autopsy the stomach was found to be distended by a very large blood clot and the small intestine and the large intestine were filled with fresh blood. The entire mucosa was dark red. No changes at site of anastomosis. The source of bleeding could not be found.

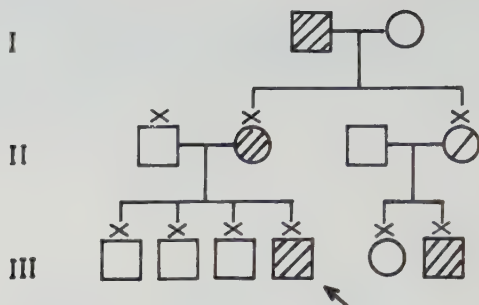
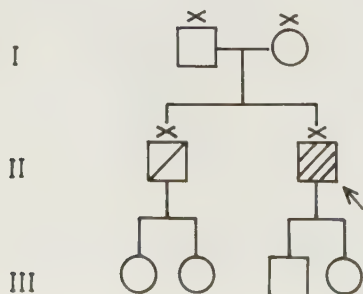
Family 92



92 III:1 AM

Trauma. — Prolonged bleeding after triple vaccination and after puncture for carotis angiography. On last occasion she bled for more than one day. Given 150 ml F I-O.

Family 93



100 III:4 AS

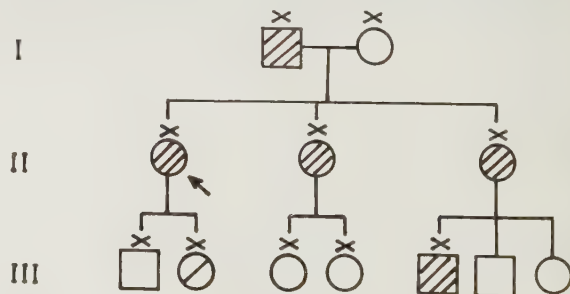
Post-extraction haemorrhage. — At 3 years dental treatment at two sittings under protection of 4x100 ml F I-O each time. No abnormal bleeding. — At 6 years tooth extraction under protection of 200 ml F I-O before and 100 ml on day after op. No abnormal bleeding. About 1 week later severe bleeding from extraction cavity, which was controlled by administration of a further 400 ml F I-O.

100 I:1 GL

Gastro-intestinal. — At 34 years gastric bleeding. — At 61 years hospitalised under the diagnosis of duodenal ulcer with melaena. No notes about roentgen findings. Hb fell to 6.2 g/100 ml. The patient was given iron i.v.

At 63 years haematemesis and melaena which continued for several days. Despite several blood transfusions and Macrodex the patient *died* after 5 days. At autopsy the gastric mucosa was found to be reddened and vessels just above pylorus to be dilated and the mucosa was bleeding. No ulcer. The liver was enlarged with signs of stasis and clearly cirrhotic. No oesophageal varices.

Family 101

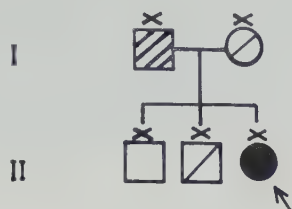


101 II:1 MO

Parturition. — Is said to have bled profusely after first 2 deliveries at 26 and 28 years. At 3rd delivery at 32 years the patient bled during the actual delivery and lost 225 ml. 4 days later profuse vaginal bleeding. Hb fell to 7.7 g/100 ml. The patient received 5 bottles of blood. Curettage produced decidua-like formation,

the size of a grape. The uterine cavity afterwards contracted and the bleeding stopped.

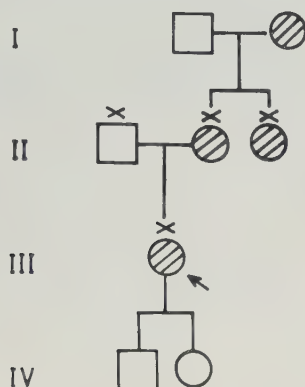
Family 103



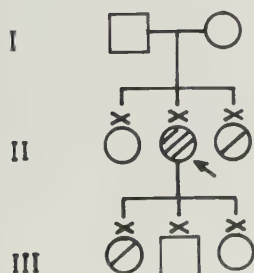
103 II:3 AW

Post-extraction haemorrhage. — At 4 years extraction of milk teeth and op. because of osteitis in upper jaw. No severe bleeding at op. but troublesome bleeding during the subsequent 2 months from the op. area. Hb fell to 7.9 g/100 ml. Several blood transfusions were given.

Family 105



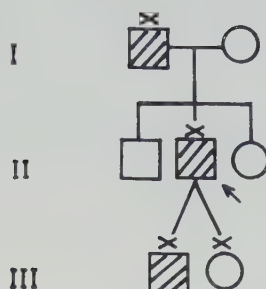
Family 107



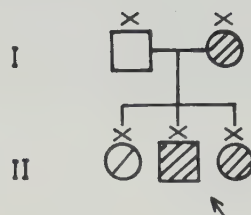
107 III:2 MB

Cholecystectomy. — At 31 years cholecystectomised. Abundant bleeding both at op. and the first few days afterwards. Hb fell to 9.5 g/100 ml. The patient received all together 6 blood transfusions. Bleeding did not stop until after transfusion of fresh blood.

Family 109



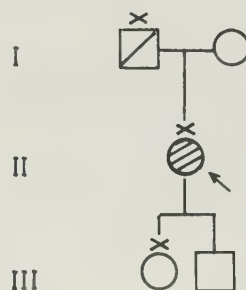
Family 111



111 II:2 T.E.

Post-extraction haemorrhage. — At 5 years severe prolonged bleeding after tooth extraction. Hb fell to 6.1 g/100 ml. Three transfusions of bank-blood and 1 transfusion of fresh blood produced only transient improvement. Finally 11 days after tooth-extraction the patient was given 2x200 ml F I-O and bleeding promptly stopped. Patient afterwards given F I-O, 100—200 ml a day for 10 days. No bleeding afterwards.

Family Bj



FREQUENCY

Improved diagnostic possibilities have resulted in a higher frequency of detection of von Willebrand's disease during the last decades. The condition has been diagnosed in various races, *e.g.* in the white race, thus also in Arabs and Jews (Salomon & Tatarski 1965) and Indians (Kasliwal *et al.* 1966) and in other races such as Negroes (Buchanan & Leavell 1956, Schulman *et al.* 1956, Arrants, Jordan & Newcomb 1962, Gomperts *et al.* 1969) and in Japanese (Yamada *et al.* 1965).

In some areas von Willebrand's disease appears to be one of the commonest inherited haemorrhagic diseases with frequencies approaching those of haemophilia (Horler & Witts 1958, Achenbach 1960, Marx & Jean 1964, Horowitz & O'Leary 1965). According to Quick (1967:a) and J. Jürgens (1969), von Willebrand's disease is even more common than haemophilia.

A search of the literature failed to reveal the frequency of von Willebrand's disease in any defined population.

PRESENT SERIES

The present material consisted of 658 persons belonging to 84 families. 603 persons were examined in further detail and 594 of them were still living on Jan. 1st 1968. These 594 were judged according to the criteria given on page 13, and the results are listed in Table 3.

Table 3

Occurrence of von Willebrand's disease in persons in the present material investigated with laboratory examinations and living on 1/1 1968

von Willebrand's disease demonstrated	255
Intermediate results (see page 13)	55
von Willebrand's disease not demonstrated	284
Sum	594

In January 1968 Sweden had a population of about 7.9 million inhabitants. This means that the frequency of von Willebrand's disease in Sweden was at least 255:7.9 million, *i.e.* 1:32,000 inhabitants.

Patients with a firm diagnosis of von Willebrand's disease were divided according to whether the disease was severe or mild, classified by the criteria on page 13. The results are given in Table 4.

Table 4

Occurrence of severe and mild von Willebrand's disease in patients in the present material investigated with laboratory examinations and living on 1/1 1968

Severe von Willebrand's disease	28
Mild von Willebrand's disease	227
Sum	255

Most of the severe cases of von Willebrand's disease had been diagnosed during the first 5 years after the disease had become more widely known in Sweden from the investigations by Nilsson *et al.* (Nilsson, Blombäck & von Francken 1957, Nilsson, Blombäck & Blombäck 1959). The severe cases not diagnosed within this period were all seen in children below 5 years.

The mild cases had naturally often not been examined so early and most of the mildest cases had not been discovered before the family investigations.

Summing up, there are probably only few undiagnosed severe cases of von Willebrand's disease in Sweden. It is difficult to say how many mild cases have remained undiagnosed, but the number is probably large. Many patients with mild von Willebrand's disease have not had any troublesome bleeding symptoms and the bleeding tendency has often not been discovered before provocation, such as by operation.

It might be of interest to compare the frequency of von Willebrand's disease with that of haemophilia. Ramgren (1962) found a frequency of 1:15,000 men in Sweden. Since there is a slight preponderance of females in the population the frequency for the entire population would be scarcely 1:30,000. According to the present calculation the frequency of von Willebrand's disease is at least 1:32,000. The frequency of mild cases is higher for von Willebrand's disease than for haemophilia, and the number of undiscovered cases is therefore probably higher for von Willebrand's disease. It is therefore probable that von Willebrand's disease is the commonest inherited haemorrhagic disease in our country.

The distribution of von Willebrand's disease in different districts and in Stockholm is given in table 5. The table is based on the last known addresses of the patients as well as on the origins of the affected branches of the families. The distribution according to their present

places of abode is more irregular. This is partly because certain families have a large number of affected members, most of whom are living in one district. This applies, above all, to family 42 in Kristianstad's län (L). It is also influenced by the nearness of the patients place of abode to a coagulation laboratory, which means an

accumulation of cases in Stockholm (A) and Stockholms län (B), Södermanlands län (D) and Malmöhus län (M). The distribution is more even when based on the original place of abode of the affected branches of the families and then agrees fairly well with the general distribution of the population.

Table 5

Number of living patients with a firm diagnosis of von Willebrand's disease and origins of their families in various counties of Sweden and in Stockholm on Jan., 1, 1968.

Code Letter	Name	Number of inhabi- tants	Number of patients	Patients per 100.000 inhabitants	Origins of families	
					Number of families	Families per 100.000 inhabitants
A	Stockholms stad	767,606	30	3.9	10	1.3
B	Stockholms län	650,661	28	4.3	5	0.8
C	Uppsala län	191,868	3	1.6	2	1.0
D	Södermanlands län	243,529	16	6.6	6	2.5
E	Östergötlands län	369,847	6	1.6	4	1.1
F	Jönköpings län	299,419	1	0.3	1	0.3
G	Kronobergs län	167,328	4	2.4	1	0.6
H	Kalmar län	236,146	0	0	0	0
I	Gotlands län	53,999	0	0	0	0
K	Blekinge län	150,897	1	0.7	2	1.3
L	Kristianstads län	264,695	38	14.3	2	0.8
M	Malmöhus län	687,910	42	6.1	13	1.9
N	Hallands län	186,025	4	2.2	1	0.5
O	Göteborgs och Bohus län	684,626	21	3.1	6	0.9
P	Älvsborgs län	391,569	8	2.0	4	1.0
R	Skaraborgs län	253,863	12	4.7	3	1.2
S	Värmlands län	286,665	13	4.5	4	1.4
T	Örebro län	272,704	12	4.4	4	1.5
U	Västmanlands län	255,264	2	0.8	1	0.4
W	Kopparbergs län	281,000	2	0.7	2	0.7
X	Gävleborgs län	294,977	2	0.7	3	1.0
Y	Västernorrlands län	277,583	2	0.7	5	1.8
Z	Jämtlands län	129,275	1	0.8	1	0.8
AC	Västerbottens län	235,230	4	1.7	2	0.9
BD	Norrbottens län	260,918	1	0.4	0	0
The whole country		7,893,704	253	3.2	82*	1.0

*) 2 of the 84 probands could be traced to Finland and Germany, respectively

INHERITANCE

Most investigators of the inheritance of von Willebrand's disease have arrived at the conclusion that the disease is autosomal dominant (von Willebrand, Jürgens & Dahlberg 1934, Matter et al. 1956, Nilsson, Blombäck & von Francken 1957, Gross & Mammen 1958, Raccuglia & Neel 1960, Achenbach 1960, Eriksson et al. 1961, Barrow & Graham 1964, Marx & Jean 1964, Cornu 1965). Some authors, however, claim to have found families, where the disease appears to be transmitted by a recessive gene, because neither of the parents of the children affected had shown signs of the disease (Schulman et al. 1955, Verstraete 1963 and Quick 1967:a). Singer and Ramot (1956) reported that several affected children had been born in consanguineous marriages without demonstrable evidence of haemorrhagic disease in the parents. Cornu (1959) made an analysis of the literature and found that of 60 probands with a probable diagnosis of von Willebrand's disease, 4 had consanguineous parents compared with at most one expected. These findings could support the opinion, that the disease is sometimes inherited recessively.

The frequency of demonstrated heredity varies from one report to another. Relatively few investigators have any personal series of several families, and the frequencies reported are usually based on compilations from the literature. Here it should be borne in mind that cases with known heredity are more likely to be published than cases without. On analysis of the literature on "Maladie de Willebrand" Revol, Favre-Gilly and Ollagnier (1950) found 82 probands: Heredity was clearly demonstrable in 57 cases, doubtful in 5 and not demonstrable in 20. Cornu (1965) reported typical heredity in 20% of the cases of von Willebrand's disease but AHF-deficiency in one or more of the direct ascendants of 80 % of the patients. Sherlock (1964) and Strauss and Bloom (1965) stressed the frequent occurrence of sporadic cases.

The penetrance and expressivity of von Willebrand's disease has often been reported to vary widely (von Willebrand 1931, Matter et al. 1956, Lehmann 1959, Achenbach 1960, Eriksson et al. 1961, Strauss & Bloom 1965 and Larrieu et al. 1968). Several investigators have found, that the disease was more common among females than among males (von Willebrand 1926, Soulier &

Larrieu 1954, Singer & Ramot 1956, Nilsson, Blombäck & von Francken 1957 and Valberg & Brown 1958) and that the clinical picture was often more severe in the females (von Willebrand 1926, Matter et al. 1956).

Graham (1959) suggested the possibility that different changes of importance for the bleeding tendency in von Willebrand's disease may be inherited separately, and then often one from the father and the other from the mother. He supported this theory partly on one of the first papers published by Nilsson et al. (Nilsson, Blombäck & von Francken 1957) on Swedish patients with von Willebrand's disease. Thus, in some of the families the mother or her relatives had a low AHF, while the father or his relatives had a prolonged bleeding time. Also other authors (Verstraete 1963, Barrow & Graham 1964, Bowie et al. 1967) have stressed that in family investigations they found reduced AHF-content and normal bleeding time in one member and a normal AHF but a prolonged bleeding time in another.

PRESENT SERIES

Mode of inheritance

In the present investigation parents, siblings and children of most of the probands were examined. In the large family 42 an autosomal dominant mode of inheritance was illustratively demonstrable. In a further 22 families the disease had been demonstrated in three consecutive generations.

In 40 families both parents of probands were examined for AHF and regarding bleeding time and often also platelet adhesiveness by the method of Salzman. The occurrence of von Willebrand's disease in the parents of these 40 probands is shown in Table 6.

Table 6

Occurrence of von Willebrand's disease in parents of 40 probands whose father and mother had both been examined

One parent	Other parent	Number of families
+	Int.	2
+	—	27
Int.	—	7
—	—	4

- + = von Willebrand's disease demonstrable
- Int. = intermediate results (definition on page 13)
- = von Willebrand's disease not demonstrable

27 families thus presented the expected pattern in autosomal dominant inheritance with one parent clearly affected and the other clearly unaffected.

Of certain interest are the two families (58 and 103), where one of the parents was affected, while the results for the other were regarded as intermediate. In those two families the father was a bleeder, but the mother also had signs of the disease. The proband in family 103 (II:3 AW) had the severe form of the disease, and it does not appear unreasonable to suppose that she was homozygous in respect of the gene for the haemorrhagic diathesis. In family 58, however, the proband (III:9 AP) had the mild form of the disease, and it appears less likely that he should have inherited the disease from both parents.

Investigation of the parents lent further support to the opinion that von Willebrand's disease is transmitted dominantly yet with incomplete penetrance. It appears less likely that the disease is transmitted alternately by a dominant and a recessive gene. But three of our probands have consanguineous parents (fam. 12, fam. 17 and fam. 25). The proband in family 12 has the severe form of the disease.

Frequency of demonstrated heredity

Frequency of demonstrated heredity for the probands in the present material is apparent from Table 7.

Table 7

Frequency of demonstrated heredity in the probands

	Number of probands
von Willebrand's disease demonstrated in one of the parents	36
Disease not found with certainty in parents but in other close relatives	15
Clear anamnestic bleeding tendency in parents or close relatives, not available for lab. invest.	8
Sum	59
Signs of the disease in parents or close relatives but disease not demonstrated with certainty	15
No anamnestic or clinical signs of the disease in the family	10
In those cases with no signs of heredity, examination	

of members of the family was usually very limited because the close relatives of the proband were either dead or otherwise not available for examination.

Penetrance and expressivity

Great variation as to penetrance and expressivity was seen in the present material.

The percentage for penetrance was calculated from the investigation of parents of 40 probands (Table 6). At least one of the parents was found to be affected in 29 of the 40 families. In a further 7 families intermediate results were obtained for one of the parents. This means a penetrance of at least 73 % and of at most 90 %. Examination of 52 children of probands has given the results seen in Table 8.

Table 8

Occurrence of von Willebrand's disease in 52 investigated children of probands

	Number of children
von Willebrand's disease demonstrated	15
Intermediate results	4
von Willebrand's disease not demonstrated	33

These figures suggest a somewhat lower penetrance: at least 58 % and at most 73 %.

The expressivity of the disease varied considerably also within one and the same family. Such was the case, for example, in family 2 with low expressivity in the sibship II:4—II:18 but much higher in the sisters III:2 and III:3.

In our patients, however, the expressivity within the sibships was more uniform than in non-relatives, as shown by a statistical test for AHF, the results of which are given in Table 9.

Table 9

Analysis of variance of AHF

Variation	df	msq
between sibships	41	322
within sibships	80	87
df = degrees of freedom		msq = mean square
F = 3.7, i.e. $p < 0.001$		

Large differences in expressivity between members of the same sibship were rare in the present material. Patients with the severe form of the disease had investigated siblings with the severe form in three cases (families 2, 4 and 13). On the other hand, only one patient with

the severe form of the disease had a sibling with the mild form (fam. 23).

The AHF-dependence of affected children on affected parents was examined with the X^2 -test. It was found that the resemblance between these parents and their children was closer than between the same parents and unrelated children. The resemblance seemed less striking than that found for siblings, but the test showed that the dependence was significant: $X^2=6.22$, $df=1$, $p<0.05$.

Expressivity in males and females

The sex distribution of the present material is given in Table 10.

Table 10

Sex distribution in the Swedish von Willebrand series

	Males	Females
Probands	34	50
Others with diagnosed von Willebrand's disease	<u>76</u>	<u>104</u>
Total	110	154
Of which severely ill	9	23

Of the probands, 22 were examined concerning their bleeding time and coagulation factors because of bleeding from the female genital tract. This might explain the preponderance of females among them. But females were also more common among other patients. Here, too, however, bleeding from the genital tract may explain why they were more often classified as bleeders. It is remarkable, however, that the frequency of the severe form of the disease was more than twice as high among females as among males. Here, the severity of the disease was based mainly on laboratory values. The difference between the sexes in these cases can hardly be ascribed to the fact that the bleeding tendency more readily produced symptoms in females. The figures were, however, small and the difference was not statistically significant.

Are prolonged bleeding time and low AHF inherited separately?

In the present material there were three families (Nos 4, 13 and 23), in which the AHF-content appeared to be abnormal in one of the parents and the bleeding time in the other. But in one case (4 III:1 DD) with prolonged bleeding time at the first examination a normal value was obtained at control. In the other two families the values for one of the parents (13 II:10 AE and 23 II:15 GW) are uncertain and unfortunately could not be checked. In some families we found sibships (29 III:2 ÅW and III:4 ÅH, 42 IV:35 RN and IV:38 MN, 59 II:2 SA and II:7 GÖ) in which one of the members had only a reduced AHF-content and another only a prolonged bleeding time. Closer analysis of these patients showed, that nearly all of them had a very mild form of the disease or that the diagnosis of the disease was doubtful. In most cases the lack of correlation between disturbance of AHF-content and of bleeding time can be ascribed to errors of the methods used. These errors make themselves felt especially in patients with values lying close to the limits of the normal ranges.

Table 11

Correlation between AHF and bleeding time

	AHF %			
Bleeding time by the method of	0-20	21-40	41-64	≥ 65
Duke $>30'$	25	7	2	
Duke $<30'$	3	27	29	10
Ivy $>30'$				
Ivy 16'-30'	2	25	59	53
Ivy $\leq 15'$ 1)		5	46	167
1) in Stockholm $\leq 12'$				

Table 11 of the relationship between AHF and bleeding times, which comprises most of the persons examined, both healthy and affected, is here of interest. It shows largely good agreement between reduced AHF and prolonged bleeding time. This concordance is convincing particularly in the severe form of the disease. Patients with a Duke bleeding time of less than 30 minutes but no determinations of the Ivy bleeding time could not be fitted into the table.

SYMPTOMATOLOGY

CONTROLS

For evaluating anamnestic haemorrhagic symptoms in suspected von Willebrand's disease, histories were taken of a number of persons without known bleeding disease or heredity.

The control series consisted of children above two years and seen at the outpatient unit of the department of pediatrics, Kristianstad central hospital, and the parents or other relatives, who had brought the children to the hospital. The series consisted of 500 persons

(63 males and 210 females above 15 years and 227 children below 15 years). The series is not ideal, but was considered acceptable for assessing the frequency of certain common haemorrhagic symptoms. Parous women were overrepresented in the group of females. Only few of the adults were above 50 years, and this may have influenced the frequency of, above all, gastrointestinal and certain postoperative haemorrhage.

The results of examination of the control series are given in Table 12.

Table 12
Frequency (%) of various sorts of bleedings among 500 persons without known haemorrhagic disease.

	+	++	+++	Sum.
Nose bleeding	2.2	2.4		4.6
Gingival bleeding	7.2	0.2		7.4
Traumatic oral and lip bleeding	0.6			0.6
Gastro-intestinal bleeding	0.2	0.2	0.2	0.6
Haematuria		0.6		
Meno-metrorrhagia	16.7 ¹⁾	8.6 ¹⁾		25.3 ¹⁾
Bleeding at delivery	9.0 ¹⁾	5.7 ¹⁾	4.8 ¹⁾	19.5 ¹⁾
Ecchymoses and haematoma	11.8 ²⁾			11.8 ²⁾
Petechiae	0.8	0.4		1.2
Bleeding from trivial sores and wounds	0.2			0.2
Joint bleeding				
Post-extraction haemorrhage	3.6	1.2		4.8
Postoperative bleeding		0.8	0.6	1.4

+ = bleeding often or profuse

++ = bleeding requiring medical, surgical or dental treatment

+++ = bleeding requiring blood transfusions

1) Calculated for females above 15 years

2) Bleeding often or profuse in the form of ecchymoses and haematomas occurred in females above 15 years with a frequency of 20.5%.

FREQUENCY OF HAEMORRHAGIC SYMPTOMS IN VON WILLEBRAND'S DISEASE

The frequency of various haemorrhagic symptoms in the present series of von Willebrand's disease is given in Table 13. Types of bleeding occurring in only three patients or less have not been included (see page 99).

For comparison the table includes the figures obtained by Buchanan and Leavell (1956) in a survey of

the literature on "pseudohemophilia". No such compilation has been published since, and it appears, that no calculation has been made of haemorrhagic symptoms in a large series of patients with a firm diagnosis of von Willebrand's disease. Broadly speaking, the frequencies in our series agree relatively well with the data given by Buchanan and Leavell.

The table also includes figures for the control series, which shows a high frequency of, above all, meno-metrorrhagia, post-partum haemorrhage and cuta-

Table 13

Frequency (%) of remarkable bleeding¹⁾ in the Swedish series of von Willebrand's disease, in Buchanan and Leavell's series and in a series of persons without known haemorrhagic disease.

	Swedish series	Buchanan & Leavell		Normal material
		Men	Women	
	264 ²⁾	95	104	500
	cases	cases	cases	cases
Nose bleeding	62.5	73	64.5	4.6
Meno-metrorrhagia	60.1 ³⁾		51	25.3 ³⁾
Post-extraction haemorrhage	51.5	28.5	36.5	4.8
Ecchymoses and haematomes	49.2			11.8
Ecchymoses		55.7	67	
Haematoma		8.5	7.5	
Bleeding from trivial sores and wounds	36.0	37	33.5	0.2
Gingival bleeding	34.8	33	36	7.4
Postoperative bleeding	28.0	19	20	1.4
Bleeding at delivery	23.3 ³⁾		10.5	19.5 ³⁾
Gastro-intestinal bleeding	14.0	24.5	9	0.6
Traumatic oral and lip bleeding	11.7			0.6
Petechiae	11.5	16	18.5	1.2
Joint bleeding	8.3	12.5	5	0
Haematuria	6.8	7.5	2	0.6
Other genital bleedings		1	7.5	
Ovarian bleeding	6.8 ³⁾			
Bleeding from tonsils	6.1			
Bleeding during shedding of teeth	4.9			
Bleeding at abortion	3.8			
Intramuscular, deep subcutaneous or submucous bleeding	2.7			
Bleeding from ears	3.0			
Haemoptysis	1.9			
Bleeding during eruption of teeth	1.5			

1) Types of bleeding occurring in 3 patients or less not included

2) Patients with a firm diagnosis of von Willebrand's disease

3) Calculated for females above 15 years

neous bleeding. It is remarkable that heavy bleeding at delivery was almost equally common among normal woman (above 15 years) as among woman with von Willebrand's disease. This may be explained largely by differences in parity between the two groups and is discussed further on page 96.

The findings in the controls showed that caution should be exercised in the evaluation of meno-metrorrhagia, loss of blood at delivery and cutaneous bleedings.

It is also clear from the table that the commonest haemorrhagic symptoms in von Willebrand's disease are nose-bleeding, cutaneous bleeding, bleeding from the

female genital tract, and profuse bleeding after tooth extraction.

The frequency in Swedish patients of different bleeding symptoms, which required blood transfusions or proved fatal are given in a separate Table (14). The cases are classified as severe or mild according to the definitions on page 13. Most of the serious haemorrhages occurred in patients with the severe form of the disease, although they constituted only a minor part of the entire material. In the patients with mild von Willebrand's disease, severe bleeding was commonest in the form of postoperative haemorrhage, meno-metrorrhagia, gastro-intestinal bleeding and post partum haemorrhage.

Table 14

Occurrence of bleeding requiring blood-transfusion or resulting in death among Swedish patients with a firm diagnosis of von Willebrand's disease.

	Type of von Willebrand's disease		Total
	Severe 32 patients	Mild 232 patients	
Postoperative bleeding	7	27	34
Meno-metrorrhagia	12	15	27
Gastro-intestinal bleeding	8	18	26
Nose-bleeding	17	5	22
Post-extraction haemorrhage	10	7	17
Bleeding at delivery	3	10	13
Traumatic oral or lip bleeding	8	1	9
Gingival bleeding	7		7
Bleeding from tonsils	7		7
Bleeding from trivial sores and wounds	5		5
Bleeding during shedding of teeth	4		4
Ovarian bleeding	5		5
Joint bleeding	2	1	3
Intracranial bleeding	2		2
Bleeding during eruption of teeth	1		1
Total	98	84	182

BLEEDING FROM DIFFERENT ORGANS

In the following description of the clinical picture bleeding from different organs will be discussed in detail.

Nose-bleeding

Nose-bleeding is thus the commonest symptom of von Willebrand's disease and occurs with a frequency of 70—80 % (Estren, Medal & Dameshek 1946, Levy 1947, Macfarlane & Simpkins 1954, Nevanlinna, Ikkala & Vuopio 1962 and Cornu 1965). The symptom is commonest during childhood and adolescence (von Willebrand 1933:a, Waller & Gross 1964 and Bowie et al. 1967).

Nose-bleeding may occur spontaneously, but some stimulating or provoking factor is often detectable. von Willebrand found his patients to have nose-bleeding fairly often if they worked in a bent posture during the warm season of the year. According to Achenbach (1960), nose-bleeding is apt to occur in patients with von Willebrand's disease, particularly after consumption of coffee and/or alcoholic beverages as well as after physical exertion, particularly in summer.

Achenbach also pointed out that nose-bleeding often occurs after surgical operation on any part of the body. Trauma as a cause of severe nose-bleeding has been reported by, for example, McCammon (1967).

Nose-bleeding may sometimes be very profuse and occasionally even fatal in patients with von Willebrand's disease (von Willebrand, Jürgens & Dahlberg 1934, Hewlett & Haden 1948, Darte 1955 and J. Jürgens 1959).

Present series

Of the present patients 165 (62.5 %) reported troublesome or recurrent nose-bleeding. 84 had sought medical advice for such bleeding. The haemorrhage had occurred most often during childhood and adolescence and had then been more severe than in later life (Fig. 4, page 105).

Profuse nose-bleeding had often occurred in our patients in association with some other bleeding manifestation, such as bleeding from the tonsils (26 III:2 EF), bleeding after rupture of the hymen (3 III:1 MH) and bleeding after miscarriage (42 II:2 GÅ).

As in Achenbach's compilation, fairly severe nose-bleeding often occurred in our patients after surgery such as tooth extraction (42 III:21 SN, III:25 SN and III:26 EN), operation because of mastoiditis (13 III:2 SE), operation because of ovarian cyst (2 III:2 YL) and hysterectomy (16 III:1 AKZ).

Many of the patients reported bleeding, sometimes fairly severe, after a blow against the nose (24 III:1 RA, 26 III:2 EF, 58 III:2 KF and 65 III:1 BS).

One woman (22 II:1 ID) had severe nose-bleeding on interruption of long term treatment with "p-pills" because of menorrhagia.

In 22 patients nose-bleeding had required blood transfusions. 17 of these patients had von Willebrand's disease of the severe type according to the definition on page 13.

Two children had died from nose-bleeding, a girl aged 6 years (4 IV:2 AB) and a boy aged 8 years (30 III:1 ÅW). In neither had von Willebrand's disease been diagnosed, but both were siblings of children in whom von Willebrand's disease was later diagnosed.

Gingival bleeding

In the medical literature on von Willebrand's disease it is practically only von Willebrand himself, who has devoted serious attention to gingival bleedings (von Willebrand & Jürgens 1933:a). According to him, gingival bleeding is more common in this disease than in any other haemorrhagic diathesis except scorbutus. The gingival tissue is often flabby and inflamed. Several of his patients had long episodes of almost continuous gingival bleeding, interfering with the intake of food and sometimes disturbing their sleep.

Gingival bleeding is common during tooth-brushing also in the population in general, especially in persons with gingivitis or parodontosis. Thus gingival bleeding on some occasion or another was often reported by our controls. 7.2 % of them had had frequent or profuse gingival bleeding during tooth-brushing, but only one of 500 had sought medical advice because of such bleeding.

Present series

Substantial gingival bleeding was reported by 92 patients (34.8 %). In many of them bleedings had occurred only during tooth-brushing. Others said that they had also occasionally bled spontaneously. Sometimes they had bled during the night and awakened in the morning to find blood on the pillow.

In the present series remarkable gingival bleeding was most common among children and young women. In the children it often occurred in association with eruption or shedding of the teeth. It was rarely serious, but 8 had bled so profusely as to require blood transfusions. In several of these cases there were contributory causes of the severe bleeding, namely eruption of tooth (8 II:1 RB), removal of tartar (33 III:2 AR) and periodontal osteitis with fistulation (103 II:3 AW). Two patients had simultaneous severe nose-bleeding (1 V:5 BT and 4 IV:2 AB).

Bleeding during eruption and shedding of teeth

In 1931 von Willebrand pointed out that physiological shedding of the teeth can cause bleeding in von Willebrand's disease. Such profuse bleeding in association with shedding of teeth has since been described by e.g. Raccuglia and Neel (1960), Bonechi and Pasero (1964) and Henrion and Cornu (1964).

Present series

Four of our patients reported bleeding during eruption of teeth (7 III:1 MA, 8 II:1 RB, 40 III:3 AMW and 64 II:1 GJ). One of these (8 II:1 RB) had profuse bleeding from surrounding gingiva, which required blood transfusion.

Bleeding in association with shedding of teeth had been noted in 12 patients, including 9 with severe von Willebrand's disease. Ten children, aged 5–12 years, had sought medical or dental advice because of such bleeding. Four of them (7 III:1 MA, 16 III:1 AKZ, 40 III:3 AMW and 103 II:3 AW) had received blood transfusions to replace the blood loss.

Traumatic oral bleeding

In von Willebrand's disease traumatic bleeding from the lips and oral cavity is fairly common in the first years of life. A search of the literature revealed 25 cases of such bleeding including 22 in children of at most 3 years of age. The bleeding often made blood transfusions necessary and was fatal in two cases, published by von Willebrand (1926) and by Gomperts et al. (1969).

Present series

Such bleeding had occurred in 31 of our cases, including 21 in which the disease was severe. The bleedings had occurred mostly in small children (see Fig. 4 page 105), who had fallen and hit themselves and sustained a small injury of a lip, of a frenulum or of the

tongue. The wounds in the tongue had then generally been caused by biting.

In 23 cases medical advice had been sought, often because the bleeding had continued for several days with substantial loss of blood and a fall of the Hb to 5–9 g/100 ml. Many of the children had been repeatedly admitted to hospital because of such bleeding. In 9 cases the haemorrhage had necessitated blood transfusions.

Tonsillar bleeding

Tonsillar bleeding has been described in only a few cases of von Willebrand's disease (Ascari, Barbieri & Gobbi 1964, Wake & McClure 1965, Lemoyne & Larrieu 1967 and J. Jürgens 1969).

Present series

Spontaneous tonsillar bleeding had occurred in 16 of our cases, including 10 with the severe form of the disease. The haemorrhage had usually occurred in association with tonsillitis. In 13 cases medical advice had been sought and in 7 blood transfusions had been given.

One patient (23 III:2 KW) had had such frequently recurrent and severe tonsillar bleeding that she had finally been subjected to tonsillectomy. The operation had been performed under protection of Fraction I-O without any complications.

Ear bleeding

Present series

Verified or probable ear bleeding had occurred in 8 of our patients. In 6 of them the haemorrhage had occurred during childhood. In 3 of them analysis of blood samples had suggested the severe type of the disease.

Three of the patients had haematotympanum, in one of them (20 III:2 KGP) with simultaneous nose-bleeding and in another (58 II:2 KF) after trauma. One boy (13 III:2 SE) had had a Hb of 5.6 g/100 ml during otitis, which had aroused the suspicion of ear-bleeding. One girl (40 III:3 AMW), was deaf on one side and the deafness was thought to be due to adhesions in the middle ear as a consequence of bleeding. Three patients (7 III:1 MA, 17 IV:1 EL and 65 III:1 BS) had had spontaneous bleeding from the ears.

Pulmonary haemorrhage

Haemoptysis is said to be uncommon in von Willebrand's disease. It is possible that it had occurred more often before von Willebrand's disease had become widely known, and when tuberculosis was a much more common disease than it has been during the last decades. Koch et al. (1957) mentioned a case of pulmonary tuberculosis with severe bleeding. Marx and Jean (1964) described a boy who had von Willebrand's disease and whose three paternal uncles had apparently died from haemoptysis. W. Perkins (1946) reported a patient with von Willebrand's disease whose paternal great-grandfather had shown signs of a bleeding tendency and who had died at 56 years from sudden pulmonary haemorrhage. A more recent case of severe haemoptysis and concomitant haemothorax of unknown origin was reported by Bowes (1969).

Present series

Five of our patients investigated had had haemoptysis. Two others had presumably died from pulmonary haemorrhage. These two were the paternal grandmother and the paternal aunt of 17 IV:5 LL, and at least the paternal grandmother was said to have had other signs of bleeding tendency, particularly nose-bleeding. Both patients had died before the investigation had been started.

Two of our other cases with haemoptysis (38 III:7 EP and 42 III:20 BN) had verified pulmonary tuberculosis.

An old man (63 II:5 GL) had massive pulmonary haemorrhage at 85 years and a Hb down to 7.8 g/100 ml. Roentgen examination showed pulmonary changes compatible with bronchiectasis.

A further two patients (11 II:1 GB and 91 II:1 MS) had had haemoptysis, but the source of bleeding had not been demonstrated. In neither of these two cases had the loss of blood been heavy.

Ecchymoses and haematoma

Cutaneous haemorrhage, mostly in the form of ecchymoses and haematoma, is a characteristic symptom of von Willebrand's disease. Ready bruisability is common; Imerslund (1949) and Cornu (1965) give as high a frequency as 100 %. This frequency must, however, be evaluated with caution, such bruisability being common also in persons without haemorrhagic disease. In the present control series it was reported by as many as 20.5 % of the females above 15 years.

Present series

130 patients in the present series (49.2 %) reported that they bruised very readily. 13, including 9 with the severe form of von Willebrand's disease, had sought medical advice because of severe or numerous haematomas.

In many of our patients ready bruisability was the symptom that had first drawn attention to the increased bleeding tendency.

Petechiae

Petechiae are less common in von Willebrand's disease (Buchanan & Leavell 1956, Matter et al. 1956, Biggs & Macfarlane 1957, Achenbach 1960, Raccuglia & Neel 1960, Cornu 1965, Horowitz & O'Leary 1965).

Present series

30 (11.5 %) of our patients with von Willebrand's disease had had the symptom on some occasion. In 12 of the 30 patients the AHF was very low (less than 20%) and in 14 the bleeding time by the method of Duke was very long (more than 30 minutes).

Intramuscular, subcutaneous and submucous haemorrhages

In contrast with what is seen in haemophilia, large soft tissue haematomas are uncommon.

In those relatively few cases where the symptom has been described the AHF-values were low: between 2 and 20 % (Biggs & Macfarlane 1957, Raccuglia & Neel 1960, Ascari, Barbieri & Gobbi 1964, Lewis 1964, Wake & McClure 1965, Ponka, Monto & Welborn 1967) though not so low as in severe haemophilia. The bleeding time by the method of Duke was only moderately prolonged: 7 minutes—28 minutes.

Present series

Only 8 patients in the present series had had known intramuscular or large subcutaneous or submucous haemorrhages.

Most impressive was the bleeding in the floor of the mouth in 16 III:1 AKZ following life-threatening menorrhagia, which had required several blood transfusions. The bleeding occurred around a carious tooth and spread in the floor of the mouth and threatened to obstruct the larynx.

One patient (6 IV:2 RF) had a large inguinal haematoma with stasis in the entire leg after puncture of the

femoral vein. 13 III:2 SE had had intramuscular bleeding in the calf, when he had been run into by an auto-cycle. These were the only patients in whom intramuscular bleeding had been caused by known external trauma.

Seven patients who had had large soft tissue haematomas also had very low mean AHF values (less than 10 %). This suggests that the mechanism underlying the bleeding may have been similar to that in haemophilia. Also the bleeding time by the method of Duke had, however, been very prolonged (more than 30 minutes).

Traumatic haemorrhage

Bleeding from trivial wounds and injuries and after puncture

Prolonged bleeding from small wounds was described as characteristic of the disease already by von Willebrand (1933:a). He described such bleeding as more severe than in thrombocytopenia. This type of bleeding is also to be expected in a disease in which a prolonged bleeding time is one of the most important examination findings. The frequencies vary from one series to another up to 100 % (Levy 1947, Imerslund 1949). It is difficult to assess the severity of the symptom because the evaluation is usually based only on the patient's reports.

Present series

95 of the Swedish patients reported prolonged bleeding from trivial wounds and injuries. In only 8 cases was medical treatment required. In 5 patients (2 III:2 YL, 4 IV:1 GB, 6 IV:2 RF, 33 III:2 AR and 48 III:1 BH), all with the severe form of von Willebrand's disease, the loss of blood was so massive as to make blood transfusions necessary.

In some of our patients severe or prolonged bleeding occurred after puncture for injection (4 IV:1 GB, 90 III:1 ML, 92 III:1 AM) or for sampling (6 IV:2 RF, 33 III:2 AR and 92 III:1 AM). In a couple of these patients (4 IV:1 GB and 6 IV:2 RF) the bleeding assumed the form of a large haematoma or soft tissue haemorrhage, while in others it was a question of prolonged oozing external bleeding. Two of the patients received blood transfusions because of the blood loss (4 IV:1 GB and 33 II:2 AR).

Bleeding after severe trauma

Remarkable bleeding after severe trauma is rare in von Willebrand's disease. A few cases of relevant

Table 15
Cases from the literature with profuse bleeding after trauma

Author	Patient	Injury	Haemorrhage
Klesper & Achenbach 1957	Female 9 years	Rammed	Life-threatening
Kyle & Baker 1964	Male, 17 years	Complicated lower leg fracture with local haematoma and haematoma in knee	Pat. received 5 liters of blood
Marx & Jean 1964	Male	Fall from 7 m height	Pat. given blood-transfusions
W. Perkins 1946	Male	Skull fracture	Died from bleeding
Wake & Mc Clure 1965	Male	Fall on forehead	Haematoma that spread. Pat. given blood transfusions

interest published are given in Table 15. (Intracranial bleeding owing to trauma is discussed in the chapter on intracranial haemorrhage below).

The injuries, at least in those cases described by Klesper and Achenbach and by Marx and Jean, were so severe that they might have caused a heavy loss of blood also in persons without any bleeding tendency.

Present series

In Swedish patients severe trauma (apart from skull trauma, see below) caused massive bleeding most often, when the accident had injured serous membranes or mucosae. Thus, joint bleeding was observed in some cases after knee injury (see page 99), nose-bleeding after jaw and face injuries (page 88), and pleural bleeding after trauma of the thoracic cage (page 100).

Severe trauma had otherwise not caused any remarkable bleeding in our patients. Judging from the patients' reports and notes in their hospital records, fractures had not caused serious bleeding complications. Only in two cases (6 IV:2 RF and 13 III:2 SE) had known trauma caused intramuscular bleeding.

Bodily injuries had sometimes caused large superficial haematomas but not any fall in the blood values. Large external bleedings had occurred only in those cases described under the heading of bleeding from trivial wounds (page 90).

Intracranial haemorrhage

Intracranial haemorrhage is uncommon in von Willebrand's disease (Estren, Medal & Dameshek 1946, Lelong & Soulier 1950, Buchanan & Leavell 1956, Nevanlinna, Ikkala & Vuopio 1962 and Cornu 1965). Spontaneous meningeal bleedings with favourable

outcome have been reported by Cornu et al. (1961) and J. Jürgens (1969). The latter had seen no less than 4 cases, and all of them had had arterial aneurysms.

Schulman et al. (1956) described a case of intracranial bleeding at birth with mild residual hemiparesis. Minot (1928) published data on a 5 year old boy in whom skull trauma was followed by an extradural haematoma that was successfully evacuated under protection of two blood transfusions.

Kasliwal et al. (1957) and Koch et al. (1957) reported one case each with fatal intracranial haemorrhage, which seems to have occurred finally after severe bleeding from other organs.

Horowitz and O'Leary (1965) and Meili, Straub and Frick (1969) briefly mentioned two cases and one case, respectively, of fatal intracranial haemorrhage in relatives of patients with von Willebrand's disease. One of these patients (Meili, Straub & Frick 1969) had a skull injury after fall from a bicycle.

Of the above 12 cases, 5 were fatal. Only one of these 5 patients had a history of trauma.

Present series

Intracranial bleeding occurred in three of our patients in whom von Willebrand's disease had been firmly diagnosed. All three had the severe form of von Willebrand's disease, the bleeding time had been very long and the AHF-values very low (Table 16).

After a fall from a height of 2½ meters 7 III:1 MA had had a subdural haematoma, which had been successfully evacuated. Roentgen examination had shown no fracture. After the operation there was profuse bleeding, which was, however, controlled by blood transfusions.

Table 16

Cases of intracranial bleeding in Swedish patients with a firm diagnosis of von Willebrand's disease

Patient	Age years	Bleeding time by method of Duke	AHF %	Trauma
4 IV:1 G.B.	24	>30'	4.7	Mild blow with flat hand
7 III:1 M.A.	3	>30'	4.5	Fall from slide
13 III:3 J.I.E.	14	>30'	3.5	Fell from cycle and hit head

The other two patients had sustained only mild or moderate trauma, which had, however, proved fatal after one and eight days, respectively. In neither could any fracture be demonstrated. In one of the patients (4 IV:1 GB) there was a haematoma under the left temporal bone, in the other (13 III:3 JIE) a haematoma, the size of a hen's egg, in the right frontal lobe and small subdural haemorrhages. Neither of the patients had received any effective treatment to stop the bleeding.

In these two cases, then, relatively mild trauma had thus been fatal as it is sometimes seen in haemophilia (Ramgren 1962, Kerr 1964, Biggs & Macfarlane 1966, Blattner 1967).

A further Swedish patient who probably had von Willebrand's disease (49 II:3 AA) had died, presumably from intracranial bleeding that had occurred after "fall from a moderate height". He had never been examined regarding his bleeding and coagulation status, but he had previously had massive bleeding also from the stomach and the urinary tract. Two daughters had verified von Willebrand's disease. Autopsy was not done.

Gastro-intestinal haemorrhage

Gastro-intestinal bleeding was not common in the Åland family described by von Willebrand, but when it occurred it was frequently serious (von Willebrand 1926 and 1931, von Willebrand & Jürgens 1933:a, von Willebrand, Jürgens & Dahlberg 1934). Eriksson (1962) examined the family for bleeding from the upper gastro-intestinal tract. He found that in the last 6 generations 14 persons had died from spontaneous bleeding and in 8 of these gastro-intestinal bleeding had been the cause of death.

In most published series the frequency of gastro-intestinal bleeding is low (Estren, Medal & Dameshek 1946, Levy 1947, Imerslund 1949, Macfarlane & Simpkins 1954, Sherlock 1964, Horowitz & O'Leary 1965, Strauss & Bloom 1965 and Wake & McClure 1965), as a rule about 10 %. In their compilation of 1956 Buchanan and Leavell found a somewhat higher figure (16.5 %) as well as a higher frequency for males than for females.

When gastro-intestinal bleeding occurred, it was usually severe. Such bleeding was sometimes long and disabling and often recurrent and life-threatening (Brandstetter et al. 1966, Marx & Jean 1964, H. Perkins 1967, Stroehlein et al. 1968). Fatal haematemesis and melaena have also been reported (von Willebrand 1926 and 1931, Achenbach et al. 1959, Carré et al. 1961, Eriksson 1962, Bonechi & Pasero 1964 and Brandstetter et al. 1966).

The source of bleeding from the gastro-intestinal tract is often difficult to locate. The results of roentgen examination have often proved negative or uncertain (Weiss 1962, Salomon & Tatarski 1965, Brandstetter et al. 1966, H. Perkins 1967). Clear-cut ulcer has rarely been detected (Eriksson 1962, Laget-Corsin & Parquet-Gernez 1968). In some cases examination has revealed deformation of the duodenal bulb, suggesting previous ulcer, but not an actual crater (Eriksson 1962, Ponka, Monto & Welborn 1967, Stroehlein et al. 1968). In one case diverticuli of the colon have been found as a possible cause of intestinal bleeding (Marx & Jean 1964). In another case (Kyle & Baker 1964) laparotomy revealed bleeding longitudinal ulcerations in the cardia, so-called Mallory-Weiss syndrome.

Closer examination of the gastric mucosa revealed superficial ulcerations that had not been demonstrable in the roentgenogram of one patient who had died

(Brandstetter et al. 1966) and in one operated upon (Ponka, Monto & Welborn 1967).

In patients with gastro-intestinal bleeding but without any known bleeding disorder a clear source of bleeding is much more commonly found. Schiller, Trulove and Williams (1970) made an analysis of a large series of such haemorrhages in all together 2.149 patients at Radcliffe Infirmary in England. A source of bleeding could be traced in 73,8 % of these cases.

Severe gastro-intestinal bleeding has sometimes occurred in children, e.g. in the Åland family (Eriksson 1962). As a rule, however, it has occurred in adults, often between 40 and 60 years, when the bleeding tendency in von Willebrand's disease is otherwise less severe.

Present series

Gastro-intestinal bleeding had occurred in 37 Swedish patients with von Willebrand's disease, diagnosed at coagulation laboratories. Furthermore, 10 relatives with anamnestic bleeding tendency had had bleedings from the digestive tract. Of these 47 patients 23 were woman and 24 men.

As many as 32 of the patients required blood transfusions because of such bleedings. Heavy losses of blood occurred particularly in patients with the severe form of the disease. Severe bleeding has, however, often occurred even in patients who, judging from laboratory studies, had the mild form of disease (see Table 14, page 87).

One patient with a firm diagnosis of von Willebrand's disease of the mild type (34 III:2 IL) died from spontaneous gastric bleeding. He died after a few days' profuse bleeding despite administration of Fraction I-O (3x100 ml) and several blood transfusions. 40 I:2 GW, also with mild von Willebrand's disease, is said to have died at home in gastro-intestinal bleeding. A third patient,

who had died from gastric bleeding (100 I:1 GL) was the maternal grandfather of a proband with known von Willebrand's disease. He had also had other bleeding symptoms, and there is reason to assume that he had had the same haemorrhagic disease as the son of his daughter.

Four other persons included in this series as relatives of patients with known von Willebrand's disease, are said to have died from gastric bleeding. In one of them (76 II:3 KGA) the death certificate confirmed the cause of death. In the other three cases (34 I:1 KL and II:1 HE, 63 II:6 JL) hospital records were unavailable.

One of our patients (11 II:1 GB) had for many years had frequently recurring severe and disabling gastric bleeding, and he had been granted a sick-pension.

Only rarely was it possible to demonstrate an ulcer or some other local cause of the gastro-intestinal bleeding. Most of the patients had been examined roentgenographically at the time of the bleeding of the stomach and duodenum and often also of the oesophagus and colon and occasionally of the small intestine. The results of roentgen examination of 24 of the patients who had required blood transfusions because of gastric bleeding are given in Table 17.

Post mortem findings were known only in respect of two of the patients who had died from gastric bleeding. One of them (34 III:2 IL) was found to have suspected callous ulcer (post mortem changes made examination difficult); the other (100 I:1 GL) had widened blood vessels near the pylorus, otherwise no demonstrable source of bleeding.

11 II:1 GB, who had been disabled for many years by gastric haemorrhage, was finally subjected to surgical exploration, but no source of bleeding was found.

Table 17
Roentgen findings in 24 Swedish patients with von Willebrand's disease, who had received blood transfusions or had died because of gastro-intestinal bleeding.

	Number of patients
Ulcer demonstrated	2
Ulcer suspected	1
Deformation of bulb, gastritis or gastroduodenitis	5
Gastric polyp	1
Nothing remarkable in part of digestive tract examined	15

The age distribution of the patients in our series at the time of consultation or admission to hospital because of gastro-intestinal bleedings is given in Fig. 5, page 106. The age distribution was much wider than that of other types of bleeding and bleeding was most common between the ages of 30 and 60 years. In the adult this type of haemorrhage was more common in men (21 patients) than in woman (14 patients).

Menorrhagia and metrorrhagia

Menorrhagia is one of the commonest haemorrhagic symptoms among women with von Willebrand's disease. The frequency varies considerably from author to author. Macfarlane and Simpkins (1954) described a large family with 7 women but with only one with profuse menstruations. Cornu (1965) gave a frequency of 75 % for remarkable genital bleedings and Buchanan and Leavell (1956) 51 % of meno-metrorrhagia among women with von Willebrand's disease. The wide variation in the frequency is probably due to differences in opinion among the physicians and among the patients as to what should be regarded as severe bleeding. Anaemia, if present, is useful in deciding this point. It appears that no exact measurements have been made of the amounts of blood lost. It is of interest to compare the patients with von Willebrand's disease and our normal series, where 25.2 % of the women above 15 years reported recurrent profuse menstrual flow, 8.6% had sought medical advice because of such symptoms.

According to several authors, the profuse menstrual flow occurs, above all, among young women during the first few years after menarche (Waller & Gross 1964, Henrion 1965 and van Creveld & Shellekens 1969), and a search of the literature for life-threatening menorrhagia showed that most such cases occurred in the beginning of the period of reproduction.

Very serious profuse menstrual flow has been described by various authors (B. Jacobsson 1957, Sharp & Ellis 1960, Henrion 1965, Hill & Taylor 1968, Larrieu et al. 1968, van Creveld & Shellekens 1969, Gomperts et al. 1969 and J. Jürgens 1969). In some cases the symptom was so refractory that the women were finally subjected to hysterectomy (B. Jacobsson 1957, Sharp & Ellis 1960, Hill & Taylor 1968 and Larrieu et al. 1968).

With available therapeutic methods fatal menorrhagia is rare, but such cases have been described by e.g. Fowler (1937), J. Jürgens (1969) and von Willebrand (von Willebrand, Jürgens & Dahlberg 1934) whose first patient, Hjördis S., died from her fourth menstruation.

Present series

82 women with a firm diagnosis of von Willebrand's disease reported considerable menorrhagia or metrorrhagia. The frequency of this symptom in women above 15 years was 60.1 %.

The patient's age at the time of treatment and blood transfusion are given in Fig. 5, page 106. Our figures thus corroborate the view by Waller and Gross (1964) and Henrion (1965), for example, that menorrhagia is severest the first few years after menarche.

29 women (inclusive two, whose diagnosis had not been confirmed by laboratory examinations) were given blood transfusions because of meno-metrorrhagia.

Three girls with the severe form of von Willebrand's disease (1 V:5 BT, 4 IV:2 GB and 16 III:1 AKZ) had had such severe and often life-threatening menorrhagia so early that they had been subjected to hysterectomy or roentgen castration at 14, 15 and 16 years, respectively. One patient (36 III:19 KB) died from menorrhagia, which persisted continuously for 5 months after menarche. That death dates back to 1922, i.e. before von Willebrand's disease had been described as such. The girl was a cousin of the mother of one of our patients with the severe form of von Willebrand's disease (36 IV:2 IN).

The most serious episodes of menorrhagia occurred in patients with the severe form of the disease. But fairly profuse menstrual flow was not uncommon among other cases; at least half of the women in our series who had received blood transfusions because of menorrhagia had the mild form of von Willebrand's disease.

The course of the cases of menorrhagia that required blood transfusions is given in Table 18. Here, then, there was a tendency of the disorder, even of the severe form, to improve already before the patients had reached 20 years of age, spontaneously, after parturition or after treatment with sex hormones.

Swedish patients with von Willebrand's disease requiring blood transfusions because of menorrhagia or metrorrhagia.

1) von Willebrand's disease not confirmed by laboratory tests	
2) improvement spontaneous	5 cases
after parturition	3 "
after treatment with progesterone or "p-pills"	4 "

von Willebrand pointed out (von Willebrand, Jürgens & Dahlberg 1934) that the women in his Åland series bled less at parturition than what might have been expected. Buchanan and Leavell (1956) in their compilation of published series found an overall frequency of 10.5 % of profuse post partum bleeding for women of all ages.

This was first observed by van Creveld et al. (1962) who found an increase of the AHF in one woman from 1 % before to 15 % towards the end of pregnancy (33rd week). At the same time the bleeding time by the technique of Duke had become normal from 25 minutes before pregnancy to 3 minutes in the 33rd week.

Similar observations have later been made by *e.g.* Strauss and Diamond (1963), Kasper *et al.* (1964), Winkelmann *et al.* (1967) and Walker and Dormandy (1968). Occasionally, however, the AHF-content and bleeding time in patients with von Willebrand's disease with low values before pregnancy remained low throughout pregnancy (Winkelmann *et al.* 1967, Walker & Dormandy 1968). In such cases the women lost large amounts of blood at delivery.

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Diamond 1963, Winckelmann et al. 1967). This means that the risk of bleeding is less on the day of parturition than somewhat later.

Thus, though the frequency of heavy bleeding is not so very high, when it does occur it is often severe and may persist with exacerbations for several months. Examples of such cases have been described by Mc Cammon (1967), Winckelmann et al. (1967) and Hill and Taylor (1968). Occasionally the bleeding could only be controlled by hysterectomy (Hill & Taylor 1968) or radiotherapy (Mc Cammon 1967). Fatal bleeding at delivery has been reported by von Willebrand (1926), Levy (1947) and by Klesper and Achenbach (1957).

Bleeding at and after delivery may be normal on one occasion and abnormal on another (Imerslund 1949, Raccuglia & Neel 1960, Strauss & Diamond 1963, Henrion 1965 and Hill & Taylor 1968). As a rule the first delivery appears to involve the greatest risk. Delivery by Caesarean section may cause loss of just as much blood as delivery by the normal route (Hill & Taylor 1968).

The risk of bleeding has often been judged from determinations of the AHF and bleeding time and from the patient's history. Horowitz and O'Leary (1965) claim that if the bleeding time by the technique of Duke is normal and the AHF is more than 20 % and "if the patient has previously encountered no difficulty in similar situations" there is no reason statistically to expect bleeding complications at parturition. Walker and Dormandy (1968) ascribed the risk of bleeding above all to the low AHF-values and feel that an AHF of 30 % or less at the time of parturition is an absolute indication for prophylaxis with substitution of factor VIII in the form of fresh frozen plasma, cryoprecipitate or freeze-dried factor VIII.

Severe bleeding at parturition has, however, been reported also in women with higher AHF (Henrion & Cornu 1964, McCammon 1967).

Present series

The frequency of severe bleeding at delivery among females above 15 years in the present material was 23.3 %, compared with 19.5 % in the normal series. As previously mentioned (page 86), the high figure in the normal series can be explained partly by the fact that most of the women in that series were mothers of children seen at a pediatric outpatient department and had thus been parous. Of those parous women with von Willebrand's disease in the present series the frequency of profuse bleeding at delivery was 34.5 %.

In 6 of our women with von Willebrand's disease the changes in AHF and bleeding time during pregnancy were recorded (Table 19).

Thirteen of the women in our series had bled on all together fourteen occasions so heavily at or after delivery as to require blood transfusions. On 8 occasions the bleedings had occurred at first delivery, and in 6 this was the only delivery. The bleeding often occurred late and it was sometimes much prolonged with exacerbations several weeks after parturition (see Fig. 1).

Three of these women had the severe form of von Willebrand's disease with AHF of less than 20 % and a bleeding time by the method of Duke of more than 30 minutes. Delivery of two of them (2 III:2 YL and 36 IV:2 IN) had caused severe and prolonged bleeding despite prophylactic treatment with Fraction I-O and fresh plasma. None of the other women in the series with such severely abnormal values had given birth.

Judging from laboratory studies, 10 of the 13 women who had received blood transfusions at or after delivery

Table 19

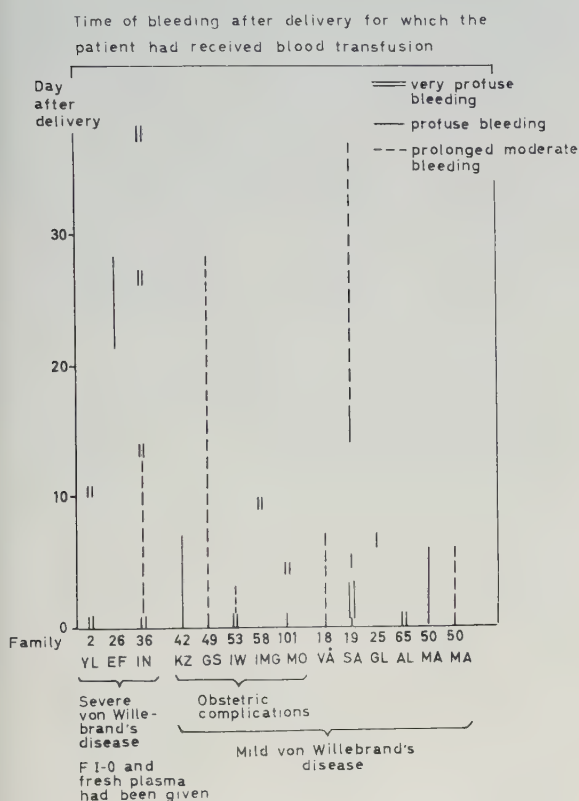
Changes of AHF-value and bleeding time during pregnancy

Patient	AHF %		Duke bleeding time	
	before pregnancy	during pregnancy	before pregnancy	during pregnancy
2 III:2 Y.L.	3-4	10 (m VIII)	60'	22' (m VIII)
22 II:1 I.D.	15-39	61 (m VII)	28 ¹⁾	14 ¹⁾ (m VII)
26 III:2 E.F.	17		60'	11'-18' (m IX)
36 IV:2 I.N.	2	4.8 (m IX)	55'-63'	30' (m IX)
42 III:19 I.H.			18'	2'33'' (m VI)
III:34 K.S.	35-45	48 (m VI)	1'-8'	6'-8' (m VI)

¹⁾ bleeding time according to Ivy

had the mild form of von Willebrand's disease. A contributory cause of the bleeding in one (42 III:27 KZ) of these cases was a large vaginal rupture. In three cases the hospital records contained notes about pieces of

Fig. 1



placenta or decidual rests at inspection or after uterine curettage (49 IV:3 GS, 58 III:1 AMG and 101 II:1 MO). One woman with the mild form of von Willebrand's disease (53 III:2 IW) had bled profusely at Caesarean section because of threatened cervical rupture. In that case the bleeding had occurred immediately after the operation and the patient had gone into shock. In 5 other cases mild von Willebrand's disease was the only explanation that could be found for the bleeding. One of these women (19 III:1 SA) had bled very profusely and required 21 blood transfusions.

In this connection it might be mentioned that 4.8 % of the females above 15 years in the control series received blood transfusions at delivery. The corresponding figure for the women with mild von Willebrand's disease was 8.6%.

Bleeding at abortion

Spontaneous abortion has been described as common in patients with von Willebrand's disease (Buchanan & Leavell 1956, Horowitz & O'Leary 1965 and McCammon 1967). Of Horowitz and O'Leary's series of 25 women with von Willebrand's disease, 11 had been pregnant on all together 34 occasions and 9 of the pregnancies had terminated in spontaneous abortion.

Profuse bleeding following spontaneous or induced abortion has been reported by Handley and Nussbrecher (1935) and Lelong and Soulier (1950), but has apparently not been life-threatening.

Present series

In view of the reports by Horowitz and O'Leary the women in our series were asked whether they had had spontaneous abortions and, if so, whether they had lost much blood. The records of 9 of 86 parous women with a firm diagnosis of von Willebrand's disease contained notes about spontaneous abortion. Three (32 III:2 SN, 59 II:2 SA and 100 II:2 MS) had had respectively 2, 4 and 3 abortions but also respectively 2, 4 and 4 live births. The other women had aborted spontaneously only once. One of them (65 III:1 BS) had repeatedly sought medical advice because of involuntary sterility. — On the whole, the frequency of spontaneous abortions in our series was not remarkably high. In Swedish women without known bleeding disease the frequency of spontaneous abortions has been estimated at 10–12 % (Pettersson 1970).

A profuse loss of blood at spontaneous abortion was reported by all together 7 women in the present series. But in two of them (42 II:2 GÅ and 73 I:2 EA) the diagnosis had not been confirmed by laboratory examinations. Bleeding was most troublesome in 42 II:2 GÅ, who had a Hb according to Sahli of less than 10 % (less than 1.6 g/100 ml) and the erythrocyte count fell to 960,000/mm³. The patient had not only uterine bleeding but also severe nose-bleeding, and it is not clear from the notes in the patient's records whether uterine or the nose-bleeding had caused the greater loss of blood.

One woman (86 III:1 AMÅ) reported that she had bled heavily at induced abortion but her hospital records could not be traced.

Ovarian bleeding

A form of bleeding that has received less space in the literature on von Willebrand's disease is ovarian bleeding or corpus luteum bleeding. Sharp and Ellis (1960) described a woman who had been admitted twice and operated upon because of haemoperitoneum in association with ruptured ovarian follicles. On neither occasion was the loss of blood severe. The patient had AHF of 18–34 % and the bleeding time by the method of Duke was repeatedly more than 15 minutes. Other similar cases have been briefly mentioned by Koch et al. (1957), Wake and McClure (1965) and Winckelmann et al. (1967). The two last mentioned authors give data on the AHF which was 5 % and less than 1 % and the bleeding time was more than 20 minutes in both.

Present series

Ovarian or follicular bleeding had been diagnosed in 9 of the present patients, including 5 on repeated occasions. In typical cases the patients had fallen ill intermenstrually with more or less severe abdominal pain and often decreasing Hb. Examination had revealed a rounded lump at the site of one of the ovaries or a swelling in the small pelvis. In three cases the diagnosis was confirmed by laparotomy. In none of the cases had laparoscopy been performed.

The ovarian bleeding had most often occurred early in reproductive life (see Fig. 5 page 106) and in 8 of 9 cases the women had the severe form of von Willebrand's disease. In 5 patients blood transfusions were given because of such bleeding. One woman (23 II:4 SW), aged 19 years, was operated upon for evacuation of corpus luteum bleeding. She continued to bleed heavily after the operation and died a few days later despite repeated transfusions. One woman (10 III:1 MCA) who had been treated with "p-pills" for some years had severe ovarian bleeding when she stopped using the pills. Another (16 III:1 AKZ), who had been subjected to hysterectomy, afterwards had such frequently recurrent and troublesome ovarian bleedings that she had continuously to take "p-pills", which gave improvement.

In the description of ovarian bleeding it might be of interest to mention a relatively high frequency of operations for ovarian cysts in our patients. It is quite possible that several of these cysts had formed as a consequence of follicular bleeding.

Bleeding from urinary tract

Haematuria is not common in von Willebrand's disease and, judging from published cases, it is seldom severe. According to J. Jürgens (1969), however, haematuria in von Willebrand's disease is just as common as in haemophilia and in three of his cases it was the indication for blood transfusions. Estren, Medal and Dameshek (1946) give a frequency of 6.3 % and Buchanan and Leavell (1956) gave 7.5 % for men and 2 % for women.

Present series

In our series haematuria was observed in 18 cases (6.8 %).

Only in one (9 III:1 ES) had it caused noticeable anaemia (Hb 7.5 g/100 ml). In two (7 III:1 MA and 8 II:1 RB) blood transfusions had been given, but evidently mainly to stop the bleeding. Recurrent gross haematuria had occurred in 4 (13 III:2 SE, 15 II:4 KS, 51 II:2 MN and 82 II:1 AT) but in none of them had the loss of blood been severe.

In one (7 III:1 MA) of the patients with gross haematuria the bleeding had on one occasion probably been due to stone. In the other cases no explanation could be offered for the bleeding. Urography had revealed nothing remarkable; nor had cystoscopy in those cases examined.

In three cases (13 III:2 SE, 15 II:4 KS and 82 II:1 AT) it was because of haematuria that the patients had been referred to the coagulation laboratory for investigation.

Joint bleeding

Joint bleeding is not common in von Willebrand's disease, which in this respect differs from classical haemophilia. This difference was pointed out already by von Willebrand and Jürgens (1933 a). Low figures have also been reported by other authors. Thus Estren, Medal and Dameshek (1946) gave 12.5 %, Biggs and Macfarlane (1957) 8 % and Buchanan and Leavell (1956) 12.5 % in men and 5 % in women.

When joint bleedings occur, they usually do so before puberty (Deshayes et al. 1967), and practically only in patients with the severe form of the disease. The AHF is low, in most cases less than 20%. Traumatic haemarthrosis, however, has occurred also in patients with higher values (Marx & Jean 1964, Deshayes 1967). Many of the patients with joint bleedings had had extremely low AHF-values down to 1–2 % and even to

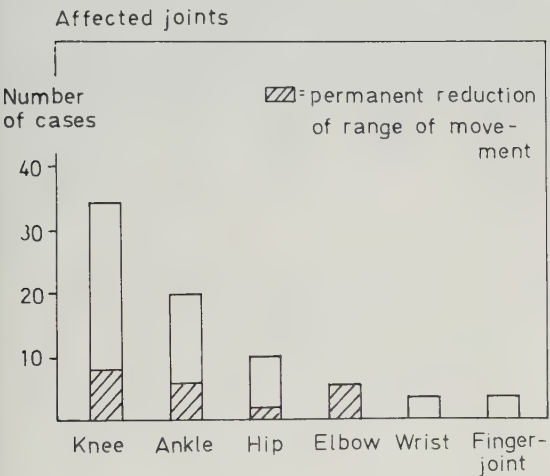
less than 1 % (Nevanlinna, Ikkala & Vuopio 1962, Verstraete 1963, Ascari, Barbieri & Gobbi 1964, Larrain & Bancalari 1965, Wake & McClure 1965, Bowie et al. 1967, Castaldi et al. 1967 and Walker & Dormandy 1968). Permanent joint deformations have been reported in only a few cases (Achenbach et al. 1959, Ascari, Barbieri & Gobbi 1964, Mauro et al. 1969, Hagedorn 1971).

Present series

Joint bleeding had been diagnosed in 18 cases and suspected in a further 4, together constituting 8.3 % of the series of patients with a firm diagnosis of von Willebrand's disease.

The knees and the ankles had been involved most often (see Fig. 2).

Fig. 2



The bleedings had occurred most often in childhood and adolescence (Fig. 5, page 106).

Of the 18 patients who had had clear symptoms of joint bleeding, 16 had the severe form of von Willebrand's disease. The bleedings had usually occurred after trivial or unknown trauma. Only in two cases had typical joint bleeding occurred in patients (14 III:4 LJ and 42 III:25 SN) with the mild form of von Willebrand's disease; in both of the cases after substantial trauma (see page 91).

In 7 patients the range of movement of joints had been permanently decreased. All had a bleeding time of more than 30 minutes by the method of Duke. The mean AHF in 3 of them had been less than 5 % and between 5 and 10 % in 3 others. For the 7th who died in 1951, the AHF had never been determined. Three

(8 II:1 RB, 9 III:1 ES and 27 III:4 KR) of these 7 patients had such joint changes that they were handicapped, though not disabled.

In all of the patients with severe joint bleeding, especially in those with permanent reduction of range of movement, roentgen examination had shown more or less severe changes with reduction of cartilage of the type seen in haemophilia.

32 patients (including 28 who are still living) in the Swedish series had the severe form of von Willebrand's disease. 16 of them clearly had joint bleeding. A further one (36 IV:2 IN) had had troublesome swelling of the joints as a child, presumably due to her haemorrhagic disease. Among such severe cases haemarthrosis is a common symptom of roughly the same frequency and severity as that in patients with corresponding AHF-level in haemophilia. In none of our patients was the AHF so low (less than 1 %) as in the haemophiliacs in Ramgren's and Ahlberg's series (1962 and 1965) regarded as severely ill.

Unusual forms of bleeding

Present series

Unusual forms of bleeding, which had occurred in at most three cases in Swedish patients with a firm diagnosis of von Willebrand's disease, are listed in Table 20.

Table 20

Unusual types of bleeding occurring in at most 3 cases in Swedish patients with a firm diagnosis of von Willebrand's disease

	Number of cases
Intracranial bleeding	3
Eye bleeding	3
Pleural bleeding	3
Coital bleeding	3
Haemorrhoidal bleeding	3
Bleeding from dental abscess	1
Cephalic haematoma (at birth)	1
Bleeding from spontaneously perforated abscess	1
Umbilical bleeding (neonatal)	1
Bleeding from oesophagus in cardiospasm	1
Retroperitoneal bleeding	1
Vaginal bleeding (at 15 months of age)	1

Intracranial bleedings are discussed on page 91–92.

Pleural bleeding was seen in one case (7 II:1 OA) after trauma with rib fracture and in another (10 III:1 MCA) in association with bleeding from a ruptured ovarian cyst. 42 III:20 BN had pulmonary tuberculosis. Thoracentesis once produced thick blood. The patient died the following day.

Eye bleeding had been caused by trauma in two (42 III:33 BAA and 72 II:3 SJ) of the three patients. In the former the intraocular bleeding had been absorbed during 5 days treatment with fresh plasma. In the latter case the bleeding had been caused by rebounding fragments while the patient was shooting with an air-gun. The bleeding occurred 5 days after the accident. The patient became almost blind on the injured side.

The retroperitoneal bleeding occurred in a severely ill patient (16 III:1 AKZ) after trauma. A lump developed in the lower abdomen and roentgen examination showed no outline of the psoas muscle. The patient had transient neurologic signs in the right leg with paresis, reduction of sensibility and reflex disorders.

In the other cases listed in the table the haemorrhage had caused no significant trouble.

Post-extraction haemorrhage

Postoperative bleeding is a common and often serious symptom in von Willebrand's disease. Such bleeding is most common after tooth extraction.

Buchanan and Leavell (1956) give a frequency of post-extraction haemorrhage of 28.5 % in males and 36.5 % in females. The frequencies are given as percentages of the entire series of patients, *i.e.* including those in whom no teeth had been extracted. von Willebrand (1931) pointed out that tooth extraction may sometimes be dangerous. Severe bleeding, requiring blood transfusions in patients with von Willebrand's disease have been reported by *e.g.* Lewis et al. (1957), Quick (1967:b), Gomperts et al. (1969) and J. Jürgens (1969). Sometimes the bleeding was prolonged with late exacerbations (Barrett 1969, Mc Ivor 1970). Lelong and Soulier (1950) reported death from severe bleeding after tooth extraction in a 4 year old sister of one of the author's probands.

Present series

Tooth extraction had been followed by profuse bleeding in 136 cases, that is in 51.5 % of all patients in the present series with a firm diagnosis of von Willebrand's disease. But only in 209 cases had tooth extraction been

performed at least once without prophylaxis with Fraction I-O or fresh plasma. Among these cases 133, that is 63.6% had had bleeding complications. 78 of the 133 patients had needed local treatment and 17 of them had in addition received blood transfusions.

The severe bleedings that required blood transfusion had occurred mostly in children and adolescents (Fig. 5 page 106 and 10 of the 17 patients had severe von Willebrand's disease.

The severe bleeding after tooth extraction did not generally cause the greatest loss of blood at the actual operation, but the blood continued to ooze during the following days with a consequent fall in Hb. An exacerbation about a week after the operation was not uncommon and was seen even in patients who had received blood transfusions prophylactically at the time of operation (6 IV:2 RF, 13 III:2 SE, 20 IV:2 KGP). In a few cases (13 III:2 SE and 103 II:3 AW) post-extraction haemorrhage had been very troublesome and persisted for several weeks with a heavy loss of blood.

Tooth extractions performed under protection of Fraction I–0 or fresh plasma are discussed on pages 122–126.

Postoperative bleeding

The frequency of profuse bleeding at or after operation in the large compilation by Buchanan and Leavell (1956) was 19 % in males and 20 % in females. These percentages refer to the entire material whether the patients had been operated upon or not. Frequencies are otherwise difficult to obtain from the literature because the number of operated cases is usually very small. Achenbach (1960) reported prolonged bleeding in 8 of 16 patients operated upon, while Valberg and Brown (1958) reported excessive bleeding in 4 of 8 patients after major operations. According to Cornu (1965), surgery in the severe form of von Willebrand's disease always implies a considerable risk of profuse bleeding. On the other hand, other authors claim that the risk of such bleeding in patients with von Willebrand's disease is relatively little (von Willebrand, Jürgens & Dahlberg 1934, Marx & Fruhmman 1958, Wegelius 1958, Eriksson 1962 and Marx & Jean 1964).

Operations on the ear, nose, throat or oral cavity have been described by several authors as causing considerable bleeding (Imerslund 1949, Achenbach 1960 and Cornu 1965). Most frequent are reports of profuse bleeding after tonsillectomy.

Operations on the digestive tract, on the other hand, are often said to be associated with only relatively little risk of bleeding in patients with von Willebrand's disease (Eriksson 1962, Cornu 1965). Operations on the stomach have been studied by Eriksson (1962) among bleeders in Åland. No serious bleeding complications occurred in any of 6 patients operated upon; this in spite of the fact that two of the patients had a serious form of the disease (very positive bleeding history, AHF-values 10–12 % and bleeding time of 33 minutes and 11 minutes, respectively by the method of Duke). Even after cholecystectomy (two cases) the course was good. But such an operation (cholecystectomy) had been associated with excessive bleeding in one patient described by Valberg and Brown (1958). — Appendectomy has mostly been performed without any abnormal loss of blood (Minot 1928, Imerslund 1949, Achenbach et al. 1959, Sharp & Ellis 1960 and Cornu et al. 1961). Serious bleeding after appendectomy has, however, been reported (Bachmann 1959, Raccuglia & Neel 1960), and in one case of the severe form of von Willebrand's disease (Arrants, Jordan & Newcomb 1962) it was life-threatening.

As for gynaecological operations, profuse bleeding has occurred, above all, after hysterectomy (B. Jacobsson 1953 and 1957, Ingram 1956, Horler & Witts 1958, Valberg & Brown 1958, Hill & Taylor 1968 and Evans 1971). According to Henrion (1965), gynaecological operations are always risky in severe cases of von Willebrand's disease but less so than oto-rhino-laryngological and stomatological operations. Profuse bleeding after uterine curettage has often been reported (B. Jacobsson 1957, Bowie et al. 1967, Mc Cammon 1967, Mathers & Castner 1967 and Quick 1967:b). Considerable loss of blood has been reported after oophorectomy in one case of severe von Willebrand's disease (Wake & Mc Clure 1965).

More or less severe postoperative bleeding has also been mentioned after therapeutic pneumothorax (Henrion & Cornu 1964), operation for obstruction of the bladder neck (Strauss & Bloom 1965), operation for herniated disk (Valberg & Brown 1958), operation for haemorrhoids (Quick 1965) and splenectomy (Little & Ayres 1928, Imerslund 1949 and Cornu et al. 1961).

Only 4 cases of fatal postoperative bleeding could be traced in the literature: after splenectomy (Little & Ayres 1928), hysterectomy (Ingram 1956), circumcision (Kasliwal et al. 1966) and pyelotomy (J. Jürgens 1969). In the last named case the patient had impaired renal

function too, which could have contributed to the serious bleeding tendency.

Present series

Postoperative bleeding in controls

In the control series described on page 85, only relatively few of the members had been operated upon, partly because many of them were children. Another control series was therefore collected at Malmö allmänna sjukhus to assess the frequency of bleeding after the following common operations: tonsillectomy, operation on the stomach, cholecystectomy and/or choledocholithotomy and finally hysterectomy. 50 randomly selected cases of each of the 4 types of operations performed in 1965 were studied regarding bleeding complications. None of the patients had any known bleeding disease. The results are given in Table 21.

Table 21

Bleeding at or after operation in patients without known bleeding disease. 50 randomly selected cases of each of 4 types of operation at Malmö allmänna sjukhus

	Bleeding			
	+++	++	+	—
Tonsillectomy	1	6	1	42
Gastric operation	15	2		33
Cholecystectomy and/or choledocholithotomy	1	1	4	44
Hysterectomy	15	4	1	30

- +++ Profuse bleeding at or after operation, requiring blood transfusion or with fatal issue
- ++ Profuse bleeding at or after operation, noted in hospital records, but no notes about blood transfusion
- + Bleeding at or after operation, noted in hospital records but apparently mild
- No notes of any bleeding at or after operation. Blood transfusions sometimes given nevertheless, especially at gastric op.

Regarding the cases marked +++ the bleeding could, as a rule, be explained by technical surgical difficulties, usually due to adhesions or malignant infiltration. Blood transfusions were mostly given during the actual operation. Transfusions after operation

were given in 11 cases including 7 cases after complicated gastric operation.

von Willebrand series

In the Swedish von Willebrand series profuse bleeding had occurred at or after operation in 74 patients with a firm diagnosis of von Willebrand's disease, i.e. 28.0 % of the patients. But only 110 of the patients had been operated upon without specific prophylaxis, and calculated on the basis of these the frequency was as high as 66.4%.

Several patients had been operated upon on more than one occasion. All together 165 operations had been performed without prophylactic Fraction I-O or fresh plasma. Profuse bleeding had been noted at 84, i.e. 50.9 % of these operations. The operations performed after prophylactic treatment are discussed on pages 119–122.

The bleeding tendency at various operations is given in Tables 22 and 23 which give the cases of severe and mild von Willebrand's disease where prophylactic measures had not been taken. The loss of blood is classified in the same way as in the control series (page 101). But in some cases the patient had reported that bleeding had been profuse, though no notes of such bleeding were found in the records. The blood loss here was classified as +. In three mild cases blood transfusions had been given though no bleeding had been stated neither by the patients nor in the records (53 III:1 SÅ: gastric op. and appendectomy, 65 II:3 LR: ablatio mammae). Here the sign used was —.

Postoperative bleeding in severe von Willebrand's disease

In cases of severe von Willebrand's disease the indications for op. were rigid, and only few patients had been operated upon. See Table 22.

In one patient (23 II:4 SW) operation of a bleeding ovarian cyst had a fatal outcome. After a similar operation another patient (2 III:2 YL) had required all together 19 bottles of blood during and after operation.

Operation for mastoiditis (13 III:2 SE) and evacuation of subdural haematoma (7 III:1 MA) had been followed by heavy loss of blood with a fall of the Hb to 4.8 and 7.2 g/100 ml, respectively.

Table 22

Bleeding at or after operation in patients with severe von Willebrand's disease. F I-O or fresh plasma not given.

	Bleeding ¹⁾			
	+++	++	+	—
<i>Operations on the ear, nose, oral cavity or throat</i>				
Operation on the nose				1
Operation on the sinus		1		
Operation behind the ear	1			
Removal of tartar	1			
Operation of the frenulum linguae		1		
<i>Gynaecological operations</i>				
Uterine curettage	2	1		
Operation of ovarian cyst	2			
<i>Other operations</i>				
Evacuation of subdural haematoma	1			
Minor skin operations		2	1	
Total	7	5	1	1

¹⁾Classified according to definitions on page 101

Three patients with the severe form of von Willebrand's disease were treated with uterine curettage because of menorrhagia. One (1 V:5 BT) of them had had severe bleeding before surgery and had not improved after the operation. In the other two (10 III:1 MA and 27 III:4 KR) the bleeding after operation was markedly increased. The Hb fell to 4.5 and 3.5 g/100 ml, respectively. Both patients received blood transfusions.

In the patients with the severe form of von Willebrand's disease also other minor operations had most often caused abundant bleeding.

Postoperative bleeding in mild von Willebrand's disease

Profuse bleeding often occurred at or after operation also in patients with mild von Willebrand's disease (Table 23). In some cases it was the profuse bleeding at surgery that had led to the diagnosis.

Analysis of the records of patients with mild von Willebrand's disease who had been operated upon without prophylaxis revealed as follows:

Removal of adenoid vegetations and/or tonsils in 26 patients, mostly children, caused profuse bleeding in

Table 23

Bleeding at or after operation in patients with mild von Willebrand's disease. F I-O or fresh plasma not given.

	Bleeding ¹⁾			
	+++	++	+	—
<i>Operations on the ear, nose, oral cavity or throat</i>				
Removal of adenoid vegetations	3	2	1	4
Tonsillectomy	2	5	2	7
Other operations		3	2	1
Sum	5	10	5	12
<i>Operations on organs belonging to the digestive tract</i>				
Gastric resection	1(+2)			1
Cholecystectomy	3	1	1	7
Appendectomy		2	2	21
Other operations	1		1	2
Sum	5(+2)	3	4	31
<i>Gynaecological operations</i>				
Hysterectomy	7	1		3
Caesarean section	1			1
Uterine curettage	2	1	5	22
Operation of ovarian cyst		1		3
Other operations	1	1	1	3
Sum	11	4	6	32
<i>Other operations</i>				
Operation of thyroid	0(+1)			1
Operation of mammae	1	1	1	3
Operation of pleura	2	2		
Prostectomy	1	2		
Operation of skeleton and joints	2	2		1
Extirpation of lipoma		2		
Eye operation		1		
Division of root (n. trigeminus)		1		
Sum	6(+1)	11	1	5
Total	27(+3)	28	16	80

Figures in brackets denote patients in whom von Willebrand's disease had not been confirmed by laboratory tests.

¹⁾Classified according to definitions on page 101. Profuse bleeding reported by the patient but not in the hospital records was classified as +.

15. The bleeding often occurred late in the postoperative course or was prolonged. Five of the patients received blood transfusions. One patient (59 III:1 TA) had such severe bleeding after tonsillectomy as to require ligation of the external carotid artery and tracheotomy.

Two deaths had occurred from bleeding after gastric resection in relatives of patients with known von Willebrand's disease. The operation had been carried out at a time when the patients were free from gastric bleeding. One (55 I:3 AK) of the patients bled profusely at the operation and continued to bleed until death three days later. The other patient (91 I:1 RS) died from sudden haemorrhage one week after the operation.

In two (70 II:1 KH and 107 III:2 MB) of 12 cases cholecystectomy had caused such heavy bleeding that the patients required 7 and 6 bottles of blood, respectively.

Appendectomy had been done in 25 cases of mild von Willebrand's disease, yet in none had the operation been attended by heavy bleeding.

Hysterectomy had caused bleeding requiring blood transfusions in 7 of 11 patients, though the operations had not been technically complicated. In some cases the bleeding had been very heavy and prolonged (60 II:10 ES, 61 III:1 ALK, 73 II:5 SE and 88 II:2 IH). In at least one of the cases (73 II:5 SE) it had been life-threatening.

Uterine curettage had been followed in one case (19 III:1 SA) by marked increase of profuse menstrual flow and a heavy blood loss and in another case (42 III:19 IH) by moderately profuse local bleeding. In both cases blood transfusions were given. No notes had been made of serious bleeding in the remaining 28 cases.

In two (28 III:4 AS and 49 III:1 AE) of 6 cases operation on the breast had caused profuse local bleeding. In one (28 III:4 AS) the local bleeding had required blood transfusion.

Less common operations were: operations on the thyroid, prostate, skeleton and joint, therapeutic pneumothorax and thoracocentesis, division of the nerve root because of trigeminal neuralgia and dacryorhinostomy. In most of these cases the bleeding tendency had been strong. In two cases it had probably been a main cause of death, namely in one case of subtotal thyroidectomy (73 I:2 EJ) and one case of thoraco-

centesis (42 III:20 BN). Operation because of trigemini neuralgia (25 IV:1 GL) had been complicated by local haemorrhage which had produced permanent neurologic symptoms.

Time of bleeding at or after operation

It is clear from the preceding section that all forms of operation in our series involved an abnormally high risk of haemorrhage. The bleeding sometimes occurred at the actual operation and sometimes a varying period afterwards.

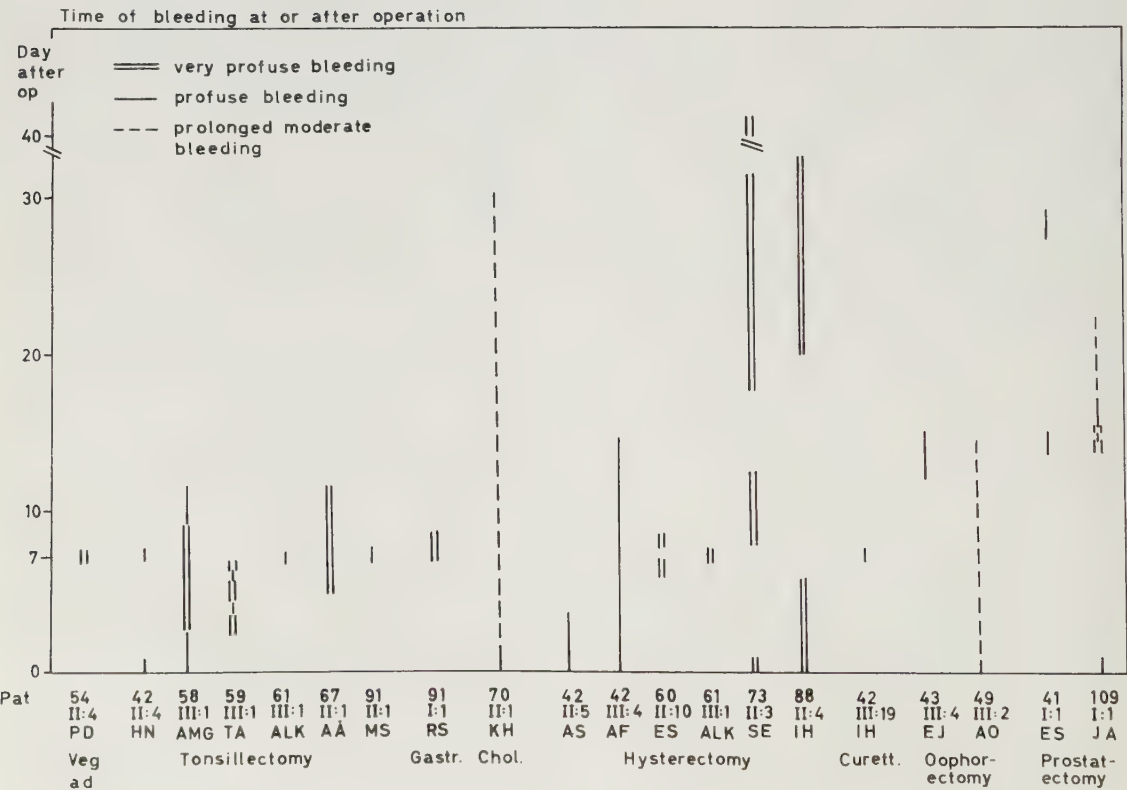
Profuse bleeding during the actual operation had occurred, for example, at operation because of

mastoiditis (13 III:2 SE), gastric resection (55 I:3 AK), cholecystectomy (81 II:7 ES and 107 III:2 MB), hysterectomy (73 II:5 SE) and dacryorhinostomy (81 II:3 NF).

In 73 II:5 SE bleeding during hysterectomy had been so severe that the patient was given as many as 6 bottles of blood during the actual operation.

However, in many of our patients the bleeding had not been so profuse on the day of operation, but had occurred or become worse several days or weeks afterwards. This was particularly the case after hysterectomy and tonsillectomy, but was also noted after other operations. A survey of cases with prolonged or late bleeding is given in Fig. 3. Compare also the situation after tooth extractions (page 100).

Fig. 3



AGE DISTRIBUTION OF BLEEDING SYMPTOMS

It is clear from the foregoing that bleeding symptoms were most common in childhood and adolescence.

Fig. 4–5 shows the age distribution of the patients at the time of medical or dental treatment for different types of bleeding. The number of occasions on which the patients received blood transfusions are indicated.

The bleeding tendency in childhood was dominated by bleeding from the nose, oral cavity and throat.

After puberty bleeding from these areas rarely required blood transfusions.

For natural reasons uterine bleeding did not occur until after puberty. Menorrhagia, however, often appeared soon after menarche and medical consultation because of such bleeding was more common between the ages of 11 and 15 years than during any other 5 year period.

Gastro-intestinal bleeding was most common in the 30–45 year age group and was also fairly common among older persons.

Fig. 4

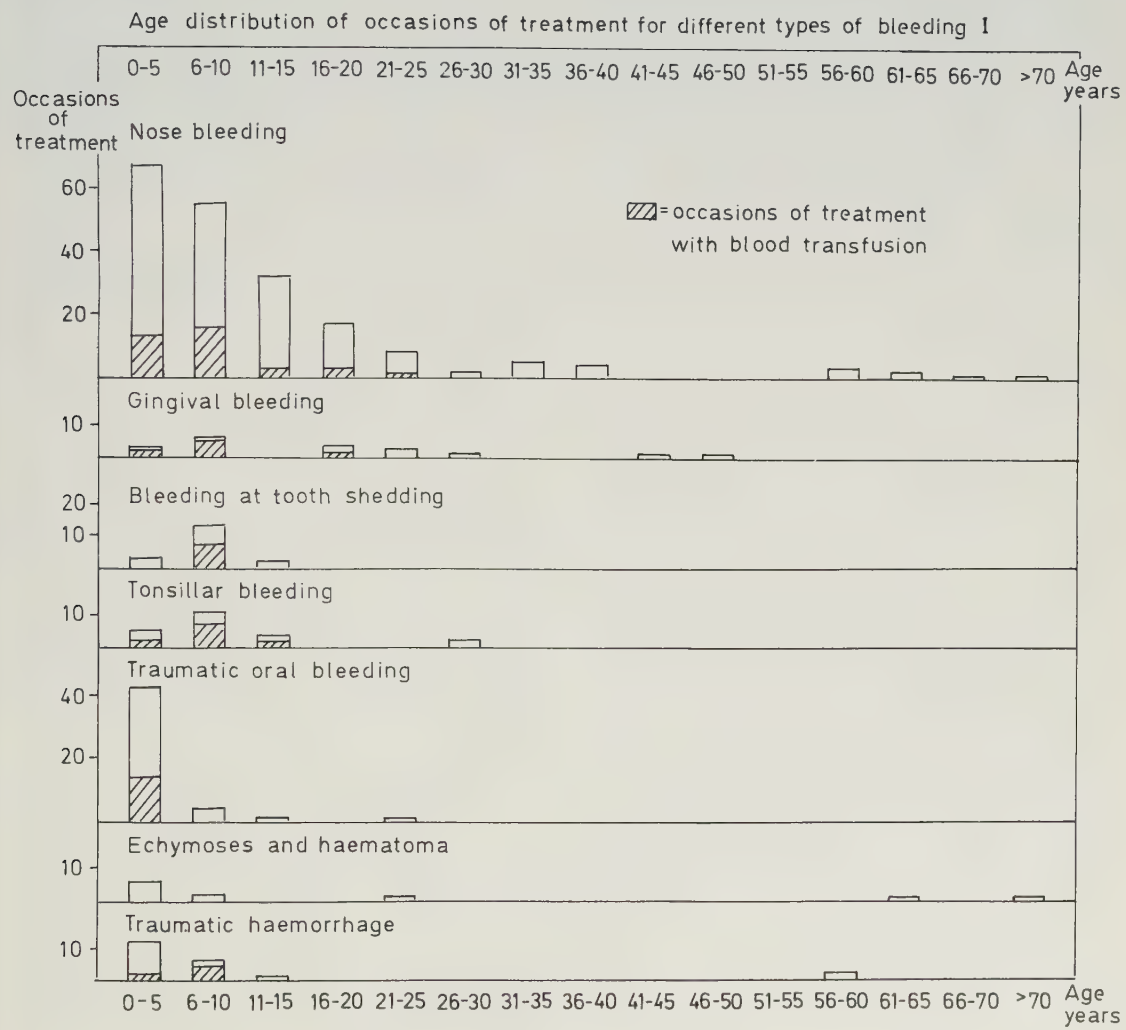
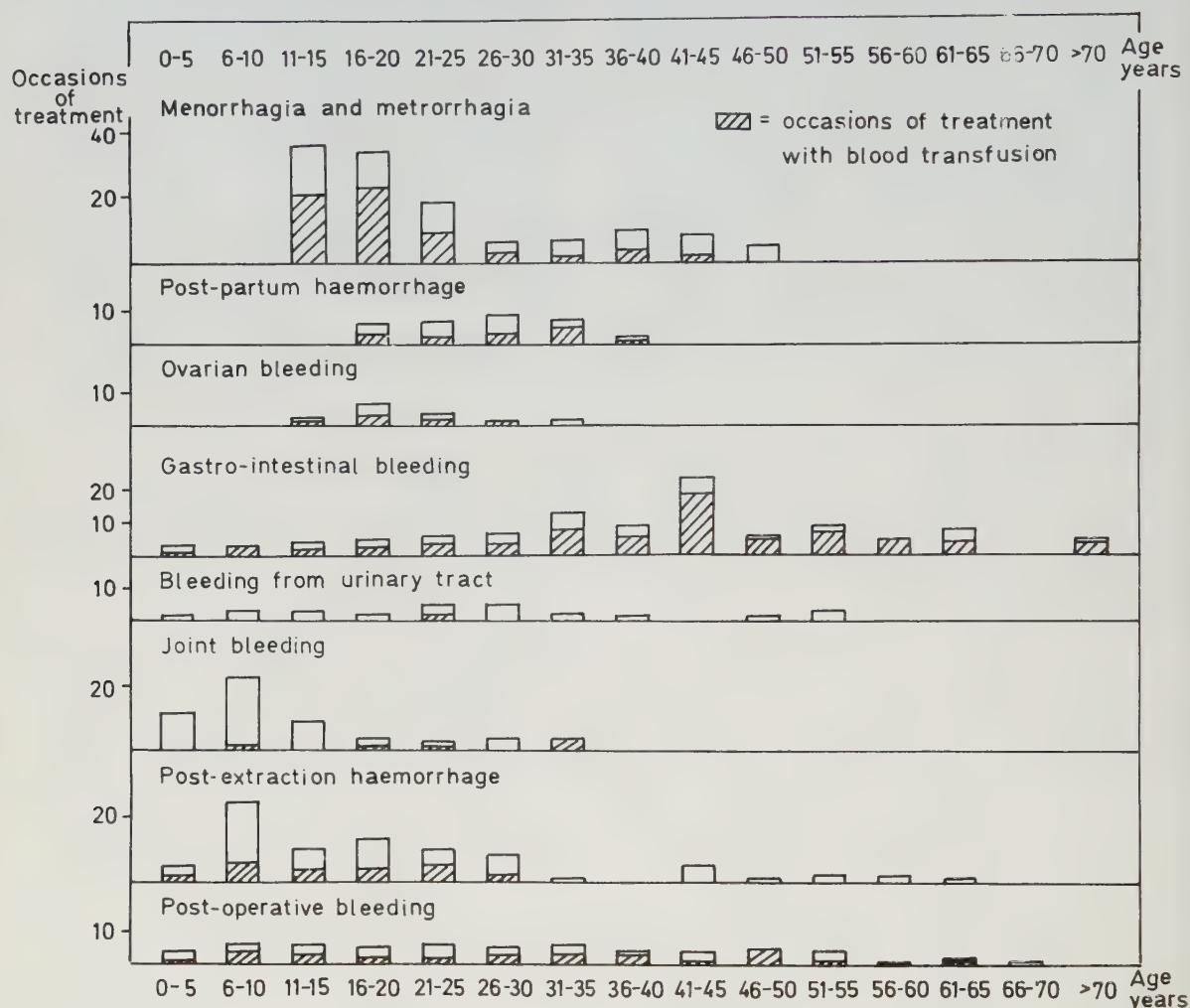


Fig 5

Age distribution of occasions of treatment for different types of bleeding II



INITIAL SYMPTOMS, DIAGNOSTIC SYMPTOMS AND AGE AT ONSET OF FIRST SYMPTOM AND DIAGNOSIS

The initial and diagnostic symptoms of the probands are summarised in Tables 24 and 25.

Here the term initial symptom is to be understood as the first bleeding symptom observed by the patient or by his or her parents. The diagnostic symptom is the bleeding symptom, that had indicated investigation at a coagulation laboratory, where von Willebrand's disease was diagnosed.

The commonest initial symptoms were nose bleeding and ready bruisability, whether von Willebrand's disease was of severe or mild type. An increased bleed-

ing tendency in severe cases sometimes was revealed very early *e.g.* by bleeding from the umbilical cord or after triple vaccination. In 7 cases of the mild type the bleeding tendency was not observed until after tooth extraction.

The diagnostic symptom was in 20 cases uterine bleeding (menorrhagia or heavy bleeding at delivery) and in two cases bleeding after hysterectomy. This may help to explain why females were so predominant among the probands (see page 84). In severe von Willebrand's disease the diagnosis was otherwise mostly made in childhood after symptoms such as nose-bleeding, ready bruisability or a general bleeding tendency. In probands with the mild form of von Wille-

Table 24

Initial symptoms in Swedish probands with von Willebrand's disease

Symptom	Type of von Willebrand's disease		
	Severe number of cases	Mild number of cases	Sum
Nose-bleeding	12	28	40
Bruisability	5	13	18
Post-extraction haemorrhage	1	7	8
Anaemia	1	3	4
Traumatic oral bleeding	2		2
Gastrointestinal bleeding	1	1	2
Haematuria		2	2
Bleeding after cuts	1	1	2
Bleeding after triple vaccination	2		2
Postoperative haemorrhage	1	1	2
Menorrhagia		1	1
Umbilical bleeding	1		1

brand's disease the diagnosis often remained concealed until bleeding was provoked by tooth extraction, for example, or other operations. In 10 patients it was a relatively late gastro-intestinal bleeding, which led to the examination resulting in the diagnosis.

The ages of the probands at the time of the initial symptoms and of the diagnosis are given in Tables 26 and 27. It was often not possible to date the initial symptom exactly, especially in the mild cases of von Willebrand's disease. In such cases the onset was described as having occurred in childhood or adolescence. It was, however, evident that the severe form of von Willebrand's disease nearly always produced manifestations in early childhood, while the bleeding tendency in the mild form of von Willebrand's disease often appeared fairly late. The diagnostic ages were therefore, on the average, much higher in the mild cases. With increasing spread of knowledge of von Willebrand's disease the severe form was practically always diagnosed before the patient was 10 years of age.

Table 26

Age at first bleeding symptom in Swedish probands with von Willebrand's disease

Table 25

Diagnostic symptoms in Swedish probands with von Willebrand's disease

Symptom	Type of von Willebrand's disease		
	Severe number of cases	Mild number of cases	Sum
Menorrhagia	7	10	17
Postoperative haemorrhage	1	11	12
Nose-bleeding	4	7	11
Gastrointestinal bleeding	1	10	11
Post-extraction haemorrhage	1	10	11
Traumatic oral bleeding		3	3
Urinary tract bleeding	1	2	3
Bleeding at delivery		3	3
Bruisability	3		3
General bleeding tendency	3		3
Anaemia	1	1	2
Gingival bleeding	1		1
Tonsillary bleeding	1		1
Bleeding after cuts	1		1
Bleeding after triple vaccination	1		1
Joint bleeding	1		1

Years	Type of von Willebrand's disease		
	Severe number of cases	Mild number of cases	Sum

0 - 5	24	9	33
6 - 10	1	5	6
Childhood	2	20	22
11 - 15		2	2
16 - 20		2	2
Adolescence		10	10
21 - 30		6	6
31 - 40		2	2
>40		1	1

Table 27

Age at diagnosis in Swedish probands with von Willebrand's disease

Years	Type of von Willebrand's disease		
	Severe number of cases	Mild number of cases	Sum
0 - 5	6	7	13
6 - 10	3	7	10
11 - 15	7	4	11
16 - 20	7	3	10
21 - 30		8	8
31 - 40	4	11	15
>40		17	17

DIAGNOSIS

In the present investigation the diagnosis of von Willebrand's disease was based mainly on the patient's history, on investigation of the family and on values found for AHF and the bleeding time according to Duke and to Ivy. As a supplementary examination method determinations were made of platelet adhesiveness by the method of Salzman. Laboratory tests were made for all probands and most of the relatives on repeated occasions. Many of the probands were examined for AHF-increase and shortening of the bleeding time following administration of Fraction I-O or fresh plasma.

The criteria for the diagnosis are given on page 13.

According to the patient's history, the bleeding tendency was classified as:

- +++ severe
- ++ moderately severe
- + slightly increased
- no increase or no certain increase

The classification of the bleeding tendency in each of the subjects examined is given in Table 2 in column *Sum*.

History

The patient's history was judged mainly from the frequency and severity of bleeding symptoms and the number of forms of bleeding in the individual case. Types of bleeding common among normals (page 85) were not considered so informative as haemorrhage of the type rarely seen in persons without any known bleeding disease. Due allowance was made for the fact that in children bleeding tendency had not had time to become manifest to the same extent as in adults.

Evaluation of the bleeding tendency in this way must, of course, be largely dependent on the subjective evaluation of the individual giving his history, the person filling in the patient's card and the person summarising the history. It was nevertheless considered warranted to summarise the findings in order to enable comparison between the anamnestic findings and the results of various laboratory tests.

AHF

The AHF-level may be influenced by several factors. For example, physical exertion raises the AHF (Rizza 1961, Egeberg 1963, Ikkala, Myllylä and Nevan-

linna 1964, Cornu 1965). Also mental stress may raise the AHF (Owren 1965). A stress-like reaction can be produced experimentally by administration of epinephrine and an increased AHF after injection of epinephrine has been observed by Egeberg (1963), for example. This observation may be important when examining children in whom sampling often causes anxiety. An increase of the AHF has also been found in women during pregnancy (page 95) and during treatment with contraceptive pills (Egeberg & Owren 1963, Nilsson & Kullander 1967, Öszoğlu & Corbacioglu 1967:a and b). Nilsson (1959) has shown that the AHF is, on the average, higher in women after the menopause than otherwise. Infections have also been found to be associated with an increase of the AHF (Egeberg 1962, Goldenfarb et al. 1970).

A slow flow of blood at sampling may result in artificially low AHF-values (Penick & Brinkhous 1956). Further, the AHF-content of the plasma decreases rapidly after sampling unless the samples are examined immediately or immediately frozen at very low temperatures (Penick & Brinkhous 1956, Rapaport, Ames & Mikkelsen 1959). Those samples from our patients, which were sent to the coagulation laboratory from distant places were centrifuged immediately, and the plasma was frozen in carbon ice and was always still frozen on its arrival at the laboratory. Nevertheless the AHF-values were more often unexpectedly low in these samples than in samples obtained directly at the coagulation laboratory with better freezing facilities.

The considerations set forth above may help to explain why the AHF-values sometimes varied from one occasion to another, mainly in patients with mild von Willebrand's disease. More or less widely varying AHF-values have also been reported by several authors (Arrants, Jordan & Newcomb 1962, Eriksson, 1962, Strauss & Bloom 1965, Abildgaard et al. 1968, Larrieu et al. 1968 and Papayannis, Wood and Israëls 1971).

It is possible that the AHF-values are also influenced by variation in the severity of the disease owing to factors other than those referred to above. In elderly patients with von Willebrand's disease the bleeding tendency diminishes (page 105) and the AHF tends to increase with age, as may be seen from the following statistical study:

AHF after more than 5 years

Of those cases in the Swedish von Willebrand-series which were re-examined after more than 5 years, 33 showed an increased AHF and only 16 a lower value. This increase was significant ($p < 0.05$). The interval between the examinations varied between 5 and 11 years and was, on the average, 6.5 years. The average increase during this period was 7%. The increase was not limited to certain AHF-levels, but was noted in patients who had originally had a high AHF-level as well as in those who had originally had a low AHF-level.

Bleeding time by the method of Duke

Determination of the bleeding time according to Duke is a relatively crude method. Buchanan and Leavell (1956), for example, have stressed the frequently considerable differences between values found for samples obtained on one and the same occasion from both ears, and such differences were seen also in our investigations.

Wide fluctuation in the bleeding time according to Duke in von Willebrand's disease from one occasion to another has often been reported (Soulier & Larrieu 1954, Cornu et al. 1961, Lemoyne & Larrieu 1967, Abildgaard et al. 1968 and others). We have seen such variation in the patients with mild von Willebrand's disease, but in patients with a severe bleeding tendency the bleeding time according to Duke has nearly always been prolonged to more than 30 minutes. The observed fluctuation may be partly explained by the sources of error of the method. But also the bleeding time, like the AHF, is influenced by pregnancy, for example, (see page 95). There may also be reason to assume that the variation of the values reflects fluctuation of the severity of the disease from one occasion to another (see page 42 and 72: 51 III:3 SÄN).

Bleeding time by the method of Ivy

In 1941 Ivy (Ivy, Nelson & Bucher 1941) described a method for determining the bleeding time of the lower arm during venous occlusion by a sphygmomanometer cuff wrapped around the upper arm. In its original form the method was more sensitive than Duke's for diagnosing certain bleeding diseases. It has, however, since been considerably improved by modifications described by Borchgrevink and Waaler 1958 and later described by Nilsson, Magnusson and Borchgrevink (1963). With these modifications the method is

much more sensitive than Duke's and it has been shown by Silver and Nilsson (1964), for example, that it can reveal an increased bleeding tendency even in mild cases of von Willebrand's disease.

The procedure, however, is difficult to standardise because of, among other things, the difficulty of producing a transverse incision of standard length and depth on the forearm. The character of the incision depends on the thickness of the skin and the elasticity of the tissues and the sharpness of the surgical blade. The bleeding time also depends on the way the blood drops are absorbed from the wound. Inadvertant contact with the edges of the incision can open the blood vessels and then bleeding may continue for more than 15 minutes even in normals. On the other hand, too cautious an absorption may result in blood drops persisting on the surface of the wound and coagulating with an artificially short bleeding time as a result. The difficulties encountered in the standardisation of the method are illustrated by, among other things, the fact that the coagulation laboratories in Malmö and Stockholm have obtained different normal values with an upper limit of 15 and 12 minutes, respectively.

In von Willebrand's disease determination of the bleeding time according to Ivy has often given different results from one occasion to another just as when the method of Duke was used (Verstraete 1963, Ascari, Barbieri & Gobbi 1964, Cornu 1965, Castaldi et al. 1967, Abildgaard et al. 1968, and Papayannis, Wood & Israëls 1971). Such variation sometimes occurred also in the mild cases in our series.

Platelet adhesiveness according to Salzman

Determinations were made of the platelet adhesiveness according to the method of Salzman in two materials. The first, limited material was collected at an international investigation in 1967. That investigation was carried out at the request of The International Committee on Haemostasis and Thrombosis when coagulation laboratories in various countries determined the platelet adhesiveness according to Salzman in order to decide the diagnostic value of the procedure in von Willebrand's disease. The Coagulation laboratory in Malmö took part in that investigation and samples were obtained from all together 61 persons with a strictly standardised material obtained from E. Salzman himself. The examination was carried

out by laboratory assistants who had been specially trained and were well versed with the method.

Of the 61 persons examined, 32 had von Willebrand's disease that had previously been diagnosed from the patients' histories and determination of the AHF and bleeding time according to Duke and Ivy. The normal material consisted of 29 persons, mainly laboratory assistants and persons married to patients with von Willebrand's disease. Two persons in the normal series were siblings of patients with von Willebrand's disease but themselves showed no evidence of the disease.

The results of this limited investigation are given in Table 28.

Table 28

Platelet adhesiveness according to Salzman: 61 persons, including 32 with known von Willebrand's disease.

Platelet adhesiveness according to Salzman %	Number	
	affected	normal
0—20	26	2
· 20		2
> 20	6	25

The two normal persons who were siblings of patients with von Willebrand's disease had normal platelet adhesiveness.

In the determination of platelet adhesiveness according to Salzman we have encountered difficulties and sources of error, especially of technical nature. The frequency of low values in both normals and affected persons proved higher in the beginning of the investigation period when the plastic tubes packed with glass beads, were 11 cm long. Later, on recommendation of Salzman, because of change in quality of the glass beads, the length of the tubes was increased to 13 cm. Then noticeably higher mean values were found and not infrequently values of more than 20% also in the affected persons. The rate of flow of the blood through the cannula proved to vary considerably with the caliber of the puncture needle, and with an increased flow rate the values found for platelet adhesiveness were much lower. An uneven flow which was slow in the beginning of sampling resulted in high values for platelet adhesiveness, even when the vacuum tube was satisfactorily filled after 45 seconds, when sampling was stopped.

Despite its imperfections the entire large material is presented here for the following reasons:

1. Thanks to its size the material may shed light on the question whether platelet adhesiveness is a factor of significance in von Willebrand's disease.
2. The investigation may reflect the value of the method and its limitations when performed by technical assistants who are not especially versed in the procedure.
3. The material has proved to be of certain interest in the calculation of correlations between platelet adhesiveness, on one hand, and historical findings, AHF-content and bleeding times, respectively, on the other.

Results of evaluation of anamnestic data and of laboratory tests

Results of evaluation of anamnestic data and various laboratory tests for all persons examined, both healthy and affected, are given in Tables 29 and 30.

Table 29

Bleeding tendency as judged from historical data		Number examined
+++		35
++		79
+		135
—		353

Table 30

Results of laboratory tests for all persons in the present material, both affected and unaffected.

Mean AHF %	Number examined
0—20	30
21—40	83
41—64	163
≥ 65	309

Mean bleeding time by method of Duke	Number examined
> 30'	36
11—30'	24
6—10'	67
≤ 5'	457

Mean bleeding time by method of Ivy	Number examined
> 30'	91
16—30'	139
≤ 15' ¹⁾	227

¹⁾ in (Stockholm ≤ 12'

Mean platelet adhesiveness according to Salzman %	Number examined
0—10	95
11—19	37
≥ 20	108

Correlations

Anamnestic data and laboratory values have been studied for correlations by various authors (Achenbach 1960, Cornu et al. 1961, Nevalinna, Ikkala & Vuopio 1962, Strauss & Bloom 1965, Larrieu et al. 1968 and Papayannis, Wood & Israëls 1971).

In a series of 37 patients Larrieu et al., for example, found a good correlation of the anamnesis with AHF and bleeding time, respectively, in severe cases of von Willebrand's disease. The correlation between anamnesis and the platelet adhesiveness according to Salzman was poorer. The correlation between AHF and bleeding time according to Duke was good in the severe cases, but poor in moderate and mild cases. Platelet adhesiveness was always abnormal, but otherwise showed no quantitative relationship to AHF or bleeding time.

Papayannis, Wood and Israëls (1971) have studied laboratory values with rank correlations. They found platelet adhesiveness according to Salzman to be inversely correlated with bleeding time according to Ivy (23 pairs, $r = -0.69$, $p < 0.001$) and positively correlated with AHF (42 pairs, $r = 0.41$, $p < 0.005$). There was a negative correlation between AHF and bleeding time, but this was not statistically significant.

Present series

In the present series anamnestic data on bleeding tendency were correlated with mean values for respectively AHF, bleeding time according to Duke, bleeding time according to Ivy and platelet adhesiveness according to Salzman (see Tables 31-34).

The tables show a clear correlation between the examination findings and the history, especially with the AHF and bleeding time according to Ivy. The bleeding time according to Duke was nearly always very long in cases with a history of several and severe bleeding symptoms, but mostly normal in those with a mild bleeding tendency and often even in those with mode-

Table 31

Correlation between historical data (bleeding tendency) and AHF				
Mean AHF %	Bleeding tendency			
	+++	++	+	-
0-20	25	4	1	
21-40	4	35	26	18
41-64	4	36	57	66
≥65		3	50	256

Table 32

Correlation between historical data (bleeding tendency) and bleeding time according to Duke.

Mean bleeding time by method of Duke	Bleeding tendency			
	+++	+-	+	-
> 30'	31	5		
11'-30'	1	16	5	2
6'-10'	1	18	23	25
≤ 5'	2	20	101	314

Table 33

Correlation between historical data (bleeding tendency) and bleeding time according to Ivy

Mean bleeding time by method of Ivy	Bleeding tendency			
	+++	++	+	-
> 30'	18	36	27	10
16'-30'	3	33	54	49
≤ 15' ¹⁾		4	37	186

¹⁾ in Stockholm ≤ 12'

rate bleeding symptoms. Bleeding time according to Ivy was sometimes prolonged to more than 30 minutes in patients with no anamnestic bleeding tendency. Determination of platelet adhesiveness according to Salzman proved less valuable than other examination methods in the evaluation of the severity of the disease.

Table 34

Correlation between historical data (bleeding tendency) and platelet adhesiveness according to Salzman

Mean platelet adhesiveness according to Salzman %	Bleeding tendency			
	+++	++	+	-
0-10	11	29	35	20
11-19	4	8	16	9
≥20	1	10	20	77

The correlations found between the results of various examination methods are given in Tables 35-39.

Table 35

Correlation between AHF and bleeding time according to Duke

Mean value of bleeding time according to Duke	Mean value of AHF %			
	0-20	21-40	41-64	≥65
> 30'	25	7	2	
11'-30'	3	12	4	5
6'-10'		15	28	22
≤ 5'	2	48	121	274

Table 37

Correlation between AHF and bleeding time according to Duke and Ivy (cases with bleeding time according to Duke of less than 30', bleeding time according to Ivy not determined, not included).

Mean value of bleeding time according to Duke > 30', Ivy > 30'	Mean values of AHF %			
	0-20	21-40	41-64	≥65
Duke > 30'	25	7	2	
Ivy 16'-30'	2	25	59	53
Ivy ≤ 15 ¹⁾		5	46	167
¹⁾ in Stockholm ≤ 12'				

Table 39

Correlation between bleeding time according to Duke and Ivy and platelet adhesiveness according to Salzman (cases with bleeding time according to Duke of less than 30', bleeding time according to Ivy not determined, not included).

Mean value (%) of platelet adhesiveness according to Salzman	Mean values of bleeding time according to			
	Duke > 30'	Duke < 30' Ivy > 30'	Ivy 16'-30'	Ivy ≤ 15 ¹⁾
0-10	11	28	36	20
11-19	4	8	13	12
≥20	1	6	31	67
¹⁾ in Stockholm ≤ 12'				

Table 36

Correlation between AHF and bleeding time according to Ivy

Mean value of bleeding time according to Ivy	Mean value of AHF %			
	0-20	21-40	41-64	≥65
> 30'	16	34	31	10
16'-30'	2	25	59	53
≤ 15 ¹⁾		5	46	167
¹⁾ in Stockholm ≤ 12'				

Table 38

Correlation between AHF and platelet adhesiveness according to Salzman

Mean value of platelet adhesiveness according to Salzman %	Mean value of AHF %			
	0-20	21-40	41-64	≥65
0-10	8	19	42	24
11-19	3	8	12	14
≥20	1	8	33	62

Statistical calculation was also made with rank correlation. Mean values for AHF and for platelet adhesiveness according to Salzman were ranked from lowest to highest values. Mean values for bleeding time were ranked as follows: Cases of bleeding time according to Duke > 30 minutes, cases of bleeding time

according to Duke < 30 minutes, according to Ivy > 30 minutes and finally values of bleeding time according to Ivy < 30 minutes arranged in a descending scale. The results of rank correlations are given in Table 40.

Table 40

Rank correlations	R	r	Number of pairs
AHF/bleeding time	0.65	0.67	427
AHF/platelet adhesiveness	0.35	0.36	227
Platelet adhesiveness/ /bleeding time	0.45	0.47	229

Here, the correlations were clearly positive ($p < 0.01$); with the highest coefficients for the correlations between AHF and bleeding time and lowest for the correlation between AHF and platelet adhesiveness according to Salzman.

General considerations

In severe cases of von Willebrand's disease the diagnosis is not difficult if facilities of a special laboratory are available. Besides a pronounced bleeding tendency in these cases the AHF is much decreased and the bleeding time by the method of Duke and by the method of Ivy is markedly prolonged.

Most of our patients, however, had mild von Willebrand's disease. Here the AHF-values were generally slightly or moderately decreased, while the bleeding time was prolonged according to Ivy but often normal according to Duke. In the mildest cases the bleeding tendency was barely noticeable or had not been noticed by the patient. The bleeding time according to the method of Duke in such cases is usually normal, and the AHF and bleeding time according to Ivy approach the limits of the normal ranges.

In a fairly large number of the persons examined, especially in relatives of the probands, certain findings were normal, while others suggested the presence of the disease in a mild form. Evaluation of such cases is made still more difficult by the above mentioned variation in the results of the tests which may be due partly to sources of error of the method and partly to a variation in the severity of the disease. It is therefore always necessary to obtain samples again and to repeat the tests to decide whether the disease is present or not, and such a decision may even then sometimes be difficult. In doubtful cases we classified the results as "intermediate."

Genetic investigations by us and by others (see page 82) have shown that the disease is inherited as an autosomal dominant. The investigations in our material of parents and children revealed a smaller number of affected persons than expected, especially if we consider only those cases where the disease had been diagnosed with certainty. It is therefore probable that most of the examined persons in whom the results obtained were "intermediate", are carriers of the gene but in whom the disease is of low expressivity and therefore has not become manifest.

In doubtful cases the diagnosis may be confirmed by administration of Fraction I-O or fresh plasma and estimation of the effect on the AHF and bleeding time, which react in a characteristic way in von Willebrand's disease (see page 7). This method was used mainly on probands in our investigation.

Differential diagnosis of von Willebrand's disease

In patients with obvious hereditary haemorrhagic disease it is often necessary to differentiate between von Willebrand's disease, mild haemophilia A, thrombasthenia and different types of primary platelet dysfunction.

The simplest method for distinguishing mild haemophilia A from von Willebrand's disease is determination of the bleeding time according to Ivy, which in haemophilia is normal. In those cases of von Willebrand's disease which have AHF-values comparable to those seen in mild haemophilia, the bleeding time according to Ivy is practically always markedly prolonged. In cases with borderline values for the Ivy bleeding time; the decision may, however, sometimes be difficult. Family investigations can often give clearcut information. Determination of platelet adhesiveness according to Salzman may also be of help in the establishment of the differential diagnosis. Another valuable method for differentiating the two diseases is administration of Fraction I-O and following up the AHF-values repeatedly for at least one day.

Difficulties encountered in the differential diagnosis between von Willebrand's disease and mild haemophilia are exemplified by the two following families (see Tables 41 and 42).

Family 63

Case	Sex	Born	Type	Bleeding history													Examinations										
				N	G	T S	T O	T E	G I	U T	M	P art.	O	E H	P	T r	J	Misc.	T E	O p.	Sum.	Date	Duke	Ivy	AHF	Sz	Remarks
																						m/year	min.	min.	%	%	
IV:16 UÖ	M	1937	Mi	1	1									1	2		2		3/63 6/67 10/68 11/70	18 2 3 5 5 3	>30 19 35 24 17 18	13 22 19 Inf. of 200 ml F I—0	26 35 24 18	26 before inf.	After inf.: 15 min. 2 hours 5 "	36 24 28 48	
II:2 NO	M	1861	Mi												1		3										
III:14 JO	M	1910	Mi												1		1										
III:21 AM	M	1922	Mi												1		3		6/43	2							
IV:2 BJ	M	1932	Mi												1		3			3		11					
IV:6 BJ	M	1938	Mi																								
IV:17 LÖ	M	1940	Mi	1											1				6/67	1 1	28	35					
IV:19 KÖ	M	1952	Mi	1											1		1		6/67	1 2	>30	19					
III:19 FÖ	F	1914	Carrier	1								1			1		2		6/67	4 8	>30	40	47				
																		10/68	2 3	15	23	26					
IV:18 HÖ	M	1913	Ni															6/67	3 2	17	85						

In family 57 bleeding symptoms had occurred in females and males, but were generally more marked in the males. The AHF-values for the male bleeders were low, as in mild haemophilia: 10–35%. The female bleeders had only slightly subnormal values, largely the same as in female carriers in haemophilia, in one case, however, as low as 29%. The bleeding time according to Ivy was normal or almost normal in nearly all the bleeders but prolonged in the proband III:2 KÅA. Platelet adhesiveness according to Salzman was examined in most of the patients. It was low in III:2 KÅA and on one occasion in one of the women. In the other affected family members the platelet adhesiveness was normal.

Administration of Fraction I—O to III:2 KÅA produced only a slight and brief increase of the AHF as in haemophilia A. It might therefore be regarded as established that the patient, like other bleeders in the family, had haemophilia¹⁾.

As for family 63, the mode of inheritance in known parts of the family suggest the presence of haemophilia. The bleeding time according to Duke for IV:16 UÖ at the first examination, however, was prolonged to 18 minutes, and the bleeding time according to Ivy was obviously prolonged in several members of the family. One of the women, III:19 FÖ, had had considerable bleeding symptoms. The investigations were supplemented in some patients with determination of platelet adhesiveness according to Salzman, which was found to be normal. — IV:16UÖ received infusion of Fraction I—O and the AHF recovered *in vivo* corresponded to the *in vitro* of infused AHF. No progressive AHF-increase occurred. This suggests that the affected family members also here had mild haemophilia¹⁾.

Glanzmann's thrombasthenia and primary platelet dysfunction are distinguished from von Willebrand's

disease by the normal values for AHF. When the AHF-values border the limit of the normal range, the differential diagnosis may sometimes be difficult. Platelet adhesiveness according to Hellem and platelet aggregation after addition of ADP, however, give abnormal values in thrombasthenia and normal values in von Willebrand's disease (Cronberg, Nilsson and Silver 1966). This also applies to clot retraction. Platelet aggregation may be studied further in Born's aggregometer after addition of ADP, collagen or epinephrine. In many primary platelet dysfunctions the aggregation curve is abnormal, while in von Willebrand's disease it is normal. In the diagnosis of platelet dysfunctions investigation of platelets in the phase contrast microscope and further determination of the content and release of platelet factor 3 may be valuable. — The effect on AHF and bleeding time after administration of Fraction I—O may contribute to a firmer diagnosis of von Willebrand's disease.

One of our patients, 19 II:I SA, had a certain disproportion between the severe bleeding symptoms and the only slightly abnormal values for AHF and bleeding time. Since the AHF-values were sometimes normal, we thought that she might have thrombasthenia or primary platelet dysfunction. Platelet adhesiveness according to Hellem was on two occasions low, 9 and 8%. Platelet aggregation according to Born, the content of platelet factor 3 and the release of this factor, however, showed normal values and clot retraction was normal. This argues against platelet dysfunction. Administration of Fraction I—O gave a characteristically retarded increase of AHF (page 27) so that the diagnosis of von Willebrand's disease may be regarded as firm.

¹⁾ The families 57 and 63 could also be examples of von Willebrand's disease type 2 according to Holmberg (page 156).

PROGNOSIS

The bleeding symptoms in patients with von Willebrand's disease are, as a rule, most pronounced during childhood and adolescence. This applies in particular to nose-bleeding, bleeding in the oral cavity and throat (page 87–88), menorrhagia (page 94) and joint bleedings (page 98). Gastro-intestinal bleeding, on the other hand, is more common in adult age (page 93).

The prognosis may otherwise be evaluated *quo ad vitam* and *quo ad valitudinem*.

Of the deaths reported in the literature available, 41 had very probably been caused by von Willebrand's disease (see Table 43). Only in 10 of these cases, however, was the diagnosis verified by laboratory tests. In the other cases the patients were close relatives of patients with verified von Willebrand's disease.

The commonest cause of death (13 cases) was gastro-intestinal bleeding. In two such cases death occurred despite intense specific therapy (Achenbach et al. 1959, Brandstetter et al. 1966).

Intracranial bleeding was fatal in 6 cases, but in two of them, reported by Kasliwal et al. (1966) and Koch et al. (1957), the bleeding occurred in the final stage following bleeding from other organs.

4 patients had died from haemoptysis, probably caused by tuberculosis (page 89) and 4 patients from postoperative bleeding (page 101).

Other forms of bleeding have rarely been fatal, especially not in recent years, during which the therapeutic possibilities have been much improved.

Severely reduced working capacity for a long time appears to have been the sequel mainly of menorrhagia in young women (Henrion 1965, Hill & Taylor 1968), and gastro-intestinal bleedings, most often in men (Marx & Jean 1964, Brandstetter et al. 1966, H. Perkins 1967, Ponka, Monto & Welborn 1967). Disabling joint bleedings of the type seen in haemophilia have not been reported.

Menorrhagia and post-partum bleeding have sometimes required hysterectomy or roentgen castration (see page 94 and 96).

PRESENT SERIES

Investigation of the Swedish patients with von Willebrand's disease showed, like the survey of the literature, that the tendency to bleeding was strongest among children and adolescents. The tendency of bleeding to decrease with increasing age is illustrated in Figs. 4–5. The figure shows also the relatively high frequency of partly serious gastro-intestinal bleeding in adult age.

Death from bleeding had occurred in 20 patients, but in only 4 of them had von Willebrand's disease been verified by laboratory studies. In the other cases the bleedings had occurred in close relatives of the probands.

The causes of death are given in Table 43 together with those found in the literature. The distribution of the various forms of bleeding was fairly equal in the two compilations.

Table 43

Deaths following different types of bleeding in von Willebrand's disease.

Type of bleeding	Literature cases Number of cases	Personal series Number of cases	Total Number of cases
Gastro-intestinal bleeding	13 (2)	7 (2)	20 (4)
Intracranial bleeding	6 (3)	3 (2)	9 (5)
Postoperative bleeding	4 (1)	4	8 (1)
Haemoptysis	4	2	6
Nose-bleeding	3	2	5
Menorrhagia	2 (2)	1	3 (2)
Traumatic lip- or mouthbleeding	2 (1)		2 (1)
Bleeding at delivery	2		2
Traumatic bleeding	2		2
Ovarian bleeding		1	1
Bleeding from varices	1		1
Bleeding of liver parenchyma	1 (1)		1 (1)
Postextraction bleeding	1		1
Total	41 (10)	20 (4)	61 (14)

Figures in brackets denote the number of cases in which von Willebrand's disease had been diagnosed before death.

Also among Swedish patients gastro-intestinal bleeding was the commonest cause of death. In one case (34 III:3 IL) the issue of such bleeding was fatal though specific treatment had been given. The quantities of available Fraction I—O proved insufficient. As elsewhere mentioned (page 129), gastro-intestinal bleeding also in patients without a bleeding disease is often serious and claims a high mortality.

Deaths from intracranial haemorrhage have occurred in three of our patients and in all of them after trauma. Two of them had a firm diagnosis of severe von Willebrand's disease (4 IV:1 GB and 13 III:3 JIE). For various reasons prophylactic treatment had not been given.

Haemoptysis with a fatal outcome had occurred in two relatives of 17 IV:5 LL. Both of them had died many years ago.

Four patients with von Willebrand's disease have died from bleeding after operation, including two after subtotal gastrectomy. In none of these 4 cases was the disease diagnosed praecoperatively and no prophylaxis had been given.

Bleedings, severely affecting working capacity have been uncommon among our patients.

One patient (11 II:1 GB) has for several years had gastric bleedings, which have recurred so often that he gradually became disabled and was granted a sick pension.

Some women (21 III:3 MÅ, 27 III:4 KR, 60 II:10 ES, 73 II:5 SE and 50 I:2 MA) have had severely anaemising menorrhagia for several years. Three women (1 V:5 BT, 4 IV:1 GB and 16 III:1 AKZ) were subjected to hysterectomy or roentgen castration soon after menarche because of severe vaginal bleeding.

In three patients with severe von Willebrand's disease (8 II:1 RB, 9 III:1 ES and 27 III:4 KR) joint bleeding caused considerable impairment of function of some joints. All three patients can, however, walk and are socially well adapted and working as a dental technician, office clerk, and housewife, respectively.

Otherwise our patients have been able to lead a largely ordinary life despite occasional severe bleeding symptoms.

Risk of von Willebrand's disease among offspring of affected patients

A question of particular interest for many patients with von Willebrand's disease is the risk of affection of offspring. The literature furnishes no answer to this question.

With an autosomal dominant mode of inheritance

the predisposition (gene) should be transmitted to 50% of children of persons affected with the disease, but, judging from the penetrance of the condition found among the parents (page 83), the risk of the children being affected is somewhat lower, about 40%. And judging from the examination of children of the probands (page 83), the risk should be still lower.

About one eighth of the patients in our material had the severe form of the disease ¹⁾. This form was probably over-represented in the material because patients with this type seek medical advice much more often than those with only mild symptoms. It would thus appear that the risk of a child of a patient with von Willebrand's disease being affected with the severe form of the disease is less than one eighth of 40%, that is less than 5%.

An AHF-dependence of affected children on affected parents was demonstrated among Swedish patients with von Willebrand's disease with a significance of $p < 0.05$ (page 84). But all of our patients with the severe form of the disease were offspring of parents with the mild form of the condition. Only 5 of those with the severe form of the disease have themselves given birth (all together 6 children). The children are still so young that they have not yet been examined with comprehensive laboratory tests. But in two of them the Duke bleeding time has been measured and has proved normal. None of the 6 children have so far shown clinical signs of bleeding tendency.

As far as AHF is concerned in our series, siblings resembled one another more closely than unrelated patients (page 83). Three probands with severe von Willebrand's disease (2 III:2 YL, 4 IV:1 GB and 13 III:2 SE) had investigated siblings who also had the severe form of the condition. Only one patient with severe von Willebrand's disease (23 II:4 SW) had a sibling with the mild form of the disease.

According to the calculations above, the risk of the bleeding disease among offspring of affected parents could thus be estimated at about 40%. The risk of a child developing the severe form of the condition is much smaller, probably less than 5%. In the estimation of the risk, knowledge of the form of the condition, *i.e.* severe or mild, of the parent appears to be of little value. However, if one child is severely ill the risk of later siblings also developing the severe form of the disease appears considerable

¹⁾ calculated on patients with a firm diagnosis of von Willebrand's disease, including those who had died before 1/1 1968.

THERAPY AND PROPHYLAXIS

Formerly treatment of bleeding in von Willebrand's disease consisted of local measures to arrest the bleeding and blood transfusions to compensate for the blood loss. Such local measures consisted of, for example, cauterisation with chromic acid for nose-bleeding, suturing of bleeding wounds and application of thrombin-saturated material to the surface of bleeding wounds.

TREATMENT WITH PLASMA AND PLASMA FRACTIONS

In the latter half of the 1950s Nilsson, Blombäck and co-workers found Fraction I—O (F I—O) from normal fresh plasma to contain a factor, the so-called von Willebrand-factor, which stimulates the production of AHF and shortens the bleeding time in von Willebrand's disease (see page 7—8 — historical). F I—O contains also AHF and fibrinogen. The von Willebrand-factor occurs also in fresh and in deep-frozen plasma, but in lower concentration than in F I—O.

Treatment with fresh plasma and F I—O has since been tried not only in Sweden (see below), but also abroad.

Good results of therapy and prophylaxis with fresh plasma for bleeding in von Willebrand's disease have been reported by *e.g.* Ponka, Monto and Welborn (1967) Mathers and Castner (1967) and Hill and Taylor (1968). In the severe form of von Willebrand's disease fresh plasma has, however, most often proved insufficient to arrest or prevent bleeding, *e.g.* at operation or delivery (Arrants, Jordan & Newcomb 1962, Walker & Dormandy 1968). In cases with a severe bleeding tendency satisfactory haemostasis requires considerable amounts of plasma, which may create circulatory problems (Henrion 1965, Cornu 1965, Rizza & Biggs 1969).

F I—O has been used in other countries mainly in association with surgery and mostly with success (Weiss 1962, Biggs & Mathews 1963, Sherlock 1964 and Castaldi *et al.* 1967). Less good results have been reported by Brandstetter *et al.* (1968) in the treatment of a patient after operation because of gastric bleeding and by Salomon and Tatarski (1965) in association with treatment of spontaneous gastrointestinal bleeding. — Cornu (1965) and Henrion (1965) stress the

difficulty encountered in the production of F I—O preparations of good quality.

In recent years patients with von Willebrand's disease have often been treated with Pool's cryoprecipitate (see page 9) and good effects of such treatment have been reported by Bennet and Dormandy (1966) Castaldi *et al.* (1967), Abildgaard *et al.* (1968), Rizza and Biggs (1969), Komp, Nclan and Carpenter (1970) and others.

PRESENT SERIES

Since 1956 many Swedish patients with von Willebrand's disease have been treated with F I—O and/or fresh plasma in the event of acute bleeding and prophylactically at delivery and operations. F I—O has been given mainly to patients with the severe form of von Willebrand's disease, but in cases of severe bleeding or at major operations also to patients with the mild form of von Willebrand's disease. Patients with the mild form of the disease are otherwise often treated with fresh plasma. Occasionally prophylaxis or treatment with fresh blood has been tried, which is otherwise used for compensating blood loss.

Prophylaxis with F I—O and fresh plasma at operations

Major operations

Seventeen of the patients in the present material have undergone all together 20 major operations under protection of F I—O or fresh plasma or both (Table 44). 8 of the operations were performed on patients with the severe form of von Willebrand's disease.

Thirteen operations, including 4 on patients with severe von Willebrand's disease, could be performed without any abnormal loss of blood. The AHF at operation in these cases was between 50 and 115% and during the first week after operation it was maintained at levels above 40%. At operation the bleeding time had been normal according to Duke (≤ 5 minutes), but during treatment after operation it sometimes varied considerably, between normal and more than 30 minutes.

In one patient (16 III:1 AKZ) with severe von Willebrand's disease hysterectomy because of life-

Major operations performed under protection of F I-0 and/or fresh plasma

Patient	Age years	Type	Operation	postoperatively		Given		Blood x 450 ml	Dur. of treatm. days	Comments
				F I-0 x 100 ml	Plasma x 400 ml	F I-0 x 100 ml	placoperatively Plasma x 400 ml			
23 III:12 KW	10	Sv	Tonsillectomy	4		16			13	
1 V:5 BT	28	Sv	Ventriculotomy	5		36			22	
103 I:1 WW	44	Mi	Gastrectomy	2		8			6	
18 III:1 VÄ	45	Mi	Cholecystectomy	3	1	11 1/2	4	4 1/2	5	3:rd -4:th day after op. fairly profuse bleeding in op.-wound
27 III:4 KR	48	Sv	Cholecystectomy + Cholecholethotomy	5		51		1	21	Diffuse bleeding in op.-field during op.
28 II:4 AS	49	Mi	Cholecystectomy	5		25 1/2	9 1/2	1	38	
101 II:2 IN	28	Mi	"	2		2			2	
101 II:1 MO	39	Mi	"	3	1 1/2				2	
31 II:4 LJ	57	Mi	Cholecholethotomy	2		2			5	
11 II:1 GB	57	Sv	Expl. laparotomy + expl. gastrotomy and enterotomy + pyloro- plasty + vagotomy	11		174		6	36	On the 4:th -8:th day after operation bleeding time according to Duke up to more than 30 min. and profuse bleeding from intestine and oozing from op.-wound.
11 II:1 GB	57	Sv	Expl. laparotomy + lysis of the small intestine	4		33			21	
1 V:5 BT	16	Sv	Hysterectomy	3		10			43	At vaginal palpation 19 days after op. vaginal rupture and profuse bleeding.
16 III:1 AKZ	15	Sv	Hysterectomy	3 1/2		104		11	35	Treatment with F I-0 discontinued after 3 days. From 6:th day after op. profuse bleeding, which later continued despite treatment with F I-0 and fresh plasma. Signs of anticoagulants.
21 III:3 MÄ	21	Mi	"	2		1			3	Postoperative infiltrates in op.-region
42 III:19 IH	50	Mi	"	4		11		4	12	Bleeding at op., 2 blood transfusions given. Treatment with F I-0 discontinued after 2 days. 5 days later profuse vaginal bleeding. Further 2 blood transfusions given.
2 III:2 YL	28	Sv	Salpingo-oophorectomy	2	2	37	28	2	27	At. op. numerous adhesions. Profuse bleeding at op. and one week later. Pat. received 1 + 1 blood transfusions.
43 IV:4 EJ	53	Mi	"		2		5		7	
73 II:5 SE	41	Mi	Oophorectomy	1 1/2	2	10	6		14	
60 II:10 ES	35	Mi	Op. of astrocytoma		10		13		14	Local bleeding during the first few days after op. Hb decreased from 12.7 to 9.7 g/100 ml.
70 II: KH	26	Mi	Ablatio mammae	2	2		4	2	5	Postoperative orbital blood effusion.

threatening menorrhagia was attended by serious haemorrhagic complications. She was operated upon under protection of large doses of F I-O, but the treatment was discontinued already 3 days after the operation (Fig. 6). The AHF then fell (lowest level 10%), and on 6th day the patient bled heavily from the vagina. She occasionally bled profusely during the following weeks despite repeated doses of F I-O. The AHF-level fluctuated considerably. Not until 7 weeks after the operation could the patient be discharged in a good condition. Examinations showed signs of anti-coagulants during treatment as well as several years later.

Another patient, 11 II:1 GB, who likewise had the severe form of Willebrand's disease, had for many years had disabling gastro-intestinal bleeding. He was finally subjected to explorative abdominal surgery under protection of F I-O. He was in a poor general

condition because of narcomania and was found to have hypoproteinaemia with a serum protein concentration down to 4.3 g/100 ml. The AHF-level during treatment reached high levels: over 200% (Fig. 7). The first few days the bleeding time was normal, and no increased bleeding was noted at the operation or soon afterwards. On the 4th to 8th day after the operation, however, the bleeding time according to Duke was prolonged to more than 30 minutes, though the patient received continued treatment. He then bled from the intestine and there was some oozing from the operation wound. Treatment with F I-O was intensified further. the bleeding time became normal, the bleeding stopped and did not recur.

A somewhat increased bleeding tendency was observed in two further patients with severe von Willebrand's disease (2 III:2 YL and 27 III:4 KR). They had been subjected to salpingo-oophorectomy and

Fig. 6

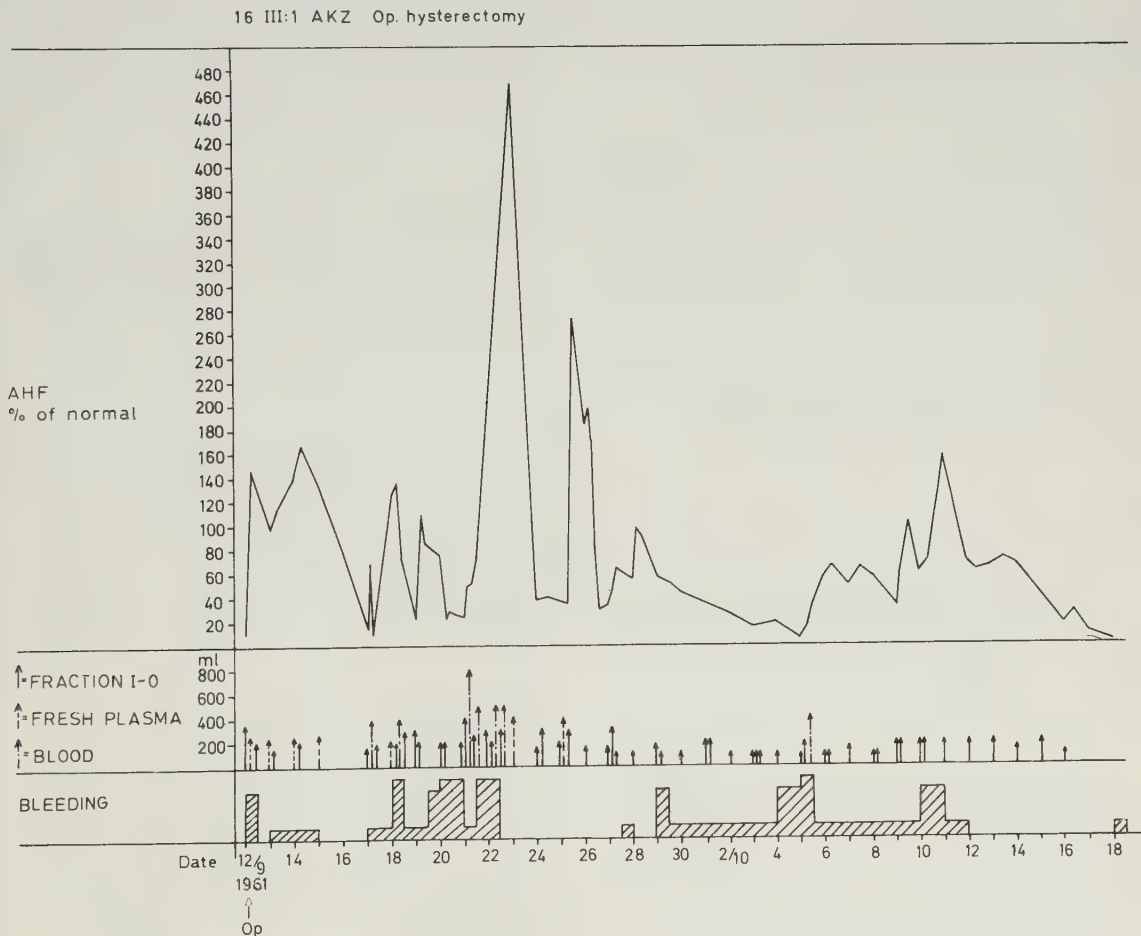


Table 45

Minor operations performed under protection of F I-0 and/or fresh plasma

Patient	Age years	Type	Operation	praeoperatively		Given		postoperatively Plasma x 400 ml	Blood x 450 ml	Dur. of treatm. days	Comments
				F I-0 x 100 ml	Plasma x 400 ml	F I-0 x 100 ml	Plasma x 400 ml				
33 III:2 AR	20	Sv	Removal of tartar	2,5		2				1 + 1	Op. in 2 sittings
29 III:1 IGK	41	Mi	Stapedectomy	2		2				2	
77 II:7 HR	23	Mi	Appendectomy		2		9			6	
81 II:3 NF	64	Mi	"	2		5				5	
75 II:1 BT	38	Mi	Op. of inguinal hernia	2		3				3	
75 II:1 BT	40	Mi	"	2		3				3	Bleeding from vagina during 2 weeks after op. Hb down to 10.6 g/100 ml.
42 III:28 KE	30	Mi	Conisation	2		1				2	
42 III:28 KE	30	Mi	Sterilisation + appendectomy								
19 II:1 SA	24	Mi	Exaeresis uteri	2	1	4	8	5		3	
29 III:1 IGK	39	Mi	Tracheostomy	1						15	
28 II:4 AS	53	Mi	Lymph node biopsy	1						1	After the last plasma infusion allergi- cal lid oedema.
75 II:1 BT	38	Mi	Meatotomy		1,5	2	3			2	
1 III:4 EK	72	Sv	Extirpation of skin tumour	5		5				3	
9 III:1 ES	23	Sv	"		1 (+ 450 ml (blood)		2			5	
29 III:1 IGK	39	Mi	Skin transplatation	1							
10 III:1 MCA	25	Sv	Pleural puncture	1		2				2	
5 III:5 PP	49	Mi	Myelography	2		2				2	
27 III:4 KR	43	Sv	Joint puncture	2		1	3			1	

Tooth extractions performed under protection of F I-0 and/or fresh plasma

Patient	Age years	Type	Extracted teeth	F I-0 x 100 ml	Praeoperatively Plasma x 400 ml	Given F I-0 x 100 ml	Postoperatively Plasma x 400 ml	Blood x 450 ml	Dur. of treatm. days	Comments
1 V:5	BT 18 BT 23 BT 23	Sv	2 molars + 8 8+, 7, -7, -8	5	3 2	1	13 17		7 10 12	Bleeding 1-3 days after op. from hole after -8, which had to be divided and levered out. Pat. received F I-0 and bleeding stopped.
III:4	EK 72	Sv	All teeth	5		4 (+ 10)			2 (+ 5)	After tooth extraction extirpation of skin tumour under continued protection of F I-0.
4 IV:1	GB 16	Sv	Tooth with granuloma	5		6		2	6	9 days after op. profuse gingival bleeding. Hb decreased to 5.1 g/100 ml
6 IV:2	RF 12	Sv	?	1					1	
8 II:1	RB 35	Sv	-6	2					1	
9 III:1	ES 20	Sv	+2, 2+		1		5	1 + 2	15	2 blood transfusions given because of post-extraction haemorrhage.
10 III:1	MCA 30	Sv	One 3:rd molar	2		5			3	
12 IV:2	KPA 19	Sv	-6	3		8		1	3	
	KPA 19	Sv	-6	3		14			5	
13 III:2	SE 23	Sv	?	2		1		2	15	
	SE 23	Sv	-6	2			20	4		Profuse bleeding 8 days after op. gave occasion to several infusions of blood and fresh plasma.
13 III:3	JIE 14	Sv	3+	1			4		5	
14 III:2	GJ 13	Mi	?	1		5			3	
	GJ 13	Mi	?	1		2	1,5 2		2	
15 II:4	KS 30	Mi	?		1				3	
24 III:1	RA 20	Sv	3:rd molar	2					1	
28 II:4	AS 46	Mi	4-, 5-, 2-, 1-, -1, -2, -4	3		11			7	
	AS 46	Mi	3+, +3, +5, +6, +7,	2		9	1		3	Profuse bleeding one day after op. Patient had received F I-0 from large batches, which had been allowed to stand over night under preparation.
28 III:2	IN 25	Mi	-8	1		1			4	
29 III:1	IGK 37	Mi	6-	2		4	5		5	
	IGK 39	Mi	-6	2		1	3		3	
33 III:2	AR 20	Sv	-7	2		13			5	Received F I-0 prepared in a modified way. Fairly profuse bleeding.
35 II:4	AR 24	Sv	5+, +5	2	2.5	1	9		9	No rise of AHF-level. Anticoagulants shown in patient's blood. Fairly profuse bleeding during several days. Lowest Hb 8.6 g/100 ml.
	PT 55	Mi	-8	3		2			2	
	PT 56	Mi	2 molars + impacted 3:rd molar	2		16			12	

Table 46 (continued)

Patient	Age years	Type	Extracted teeth	F I-0 x 100 ml	Präoperatively Plasma x 400 ml	Given F I-0 x 100 ml	Postoperatively Plasma x 400 ml	Blood x 450 ml	Dur. of treatm. days	Comments
38	58	PT	+6	2		5	2		5	
	59	PT	-7	2		9			5	
	23	MI	8+, +8	2		4			5	
	20	MI	+8		1		1		3	
40	21	MI	8+, -8		1		1		3	
	7	Sv	8+	2		1		0,5	4	
42	11	Sv	+5, +3	1	1	2	1		4	
	36	MI	?	1		2	6		4	
44	11	MI	?	2		2			5	
	33	MI	?	1		2			3	
45	14	Sv	Several teeth	1		1	4		4	
	16	Sv	+7	1	1	1	4		1	
58	16	Sv	-6	1	1	2	1		3	Pat. received also €-ACA
	20	Sv	7+	1		7			4	
	6	MI	5-	2		1			1	
	6	MI	4+	2		1	3		4	
60	6	MI	+4, +5	2			2		3	
	6	MI	5+, 4-	2			2		3	
	7	MI	+5	1		2	2		4	
	7	MI	5+, 4+	1			2		3	
61	7	MI	-4, -5	1			1		1	
	7	MI	5-	1		3	2		5	
	7	MI	4-				1,5		4	Pat. received also €-ACA
	7	MI	-8	1	1	3			4	
77	25	MI	4+, +3	1		6			6	
	12	MI	+5	1		3			3	
91	12	MI	3:rd molar	1		2			2	
	22	MI	3:rd molar	1		3			3	
100	3	MI	?	1		3			3	Bled a little
	3	MI	?	1		3			3	Bled a little
	3	MI	?	1		3			4	One week after tooth extraction pro-
	6	MI	?	2		1 + 4			11	fuse bleeding from extraction hole; stopped after infusion of F I-0.
103	5	Sv	2+, +1		0,5		0,5		1	
	7	Sv	?	1		5			3	
	7	Sv	?	1		3			3	
	9	Sv	?	1		4			6	
111	5	MI	5+	1		9			5	
	5	MI	5+	1						

Four other patients (42 IV:18 ChÅ IV:62 PS and IV:63 BIS and 73 III:2 POE) have had teeth extracted under protection of F I-0 and/or fresh plasma without bleeding complications.
No further information obtained.

BT and 9 III:1 ES) had severe von Willebrand's disease but had received prophylaxis with only fresh plasma. 13 III:2 SE, also with the severe form of the disease, had formerly bled profusely after tooth extraction under protection of fresh blood alone (see above). On a later occasion he was given a single dose of F I-O and afterwards only fresh plasma. 8 days after the operation he bled profusely and was given three blood transfusions.

Two patients (28 II:4 AS and 33 III:2 AR) had received F I—O which had not been prepared in a satisfactory way, and this could explain why it failed to produce the desired effect. The AHF-level and the bleeding time fluctuated widely during treatment.

Finally, one of these patients (35 II:4 PT) who had bled profusely after tooth extraction despite prophylaxis was found to have a circulating anticoagulant. The AHF-level was often below 10% and never exceeded 38%.

In cases of mild von Willebrand's disease with AHF of at least 45% and with a normal bleeding time according to Duke tooth extractions have been possible with careful staunching of blood without specific treatment.

Fig. 8

Prophylaxis with F I—O and fresh plasma at deliveries

Prophylaxis with F I-O and plasma before and after delivery was given to 5 of our patients including 4 with the severe form of von Willebrand's disease (See Table 47).

In two (2 III:2 YL and 36 IV:2 IN) of the patients with previously very low AHF-values delivery was complicated by profuse bleeding despite administration of F I-O and plasma.

In 2 III:2 YL delivery was complicated by primary retention of the placenta. The patient bled severely and went into shock. The shock was controlled by two blood transfusions, after which the placenta was readily removed and the bleeding stopped. Nine days later, by which time the administration of F I—O had been somewhat reduced (see Fig. 8), however, severe bleeding from the vagina recurred. The AHF-level was satisfactory (66—100%), but the bleeding time according to Duke had on various occasions during the previous days been prolonged (to more than 30 minutes). No local cause of the bleeding could be found. After administration of 600 ml F I-O together with 7x500 ml fresh blood the bleeding stopped, and the further course was uncomplicated.

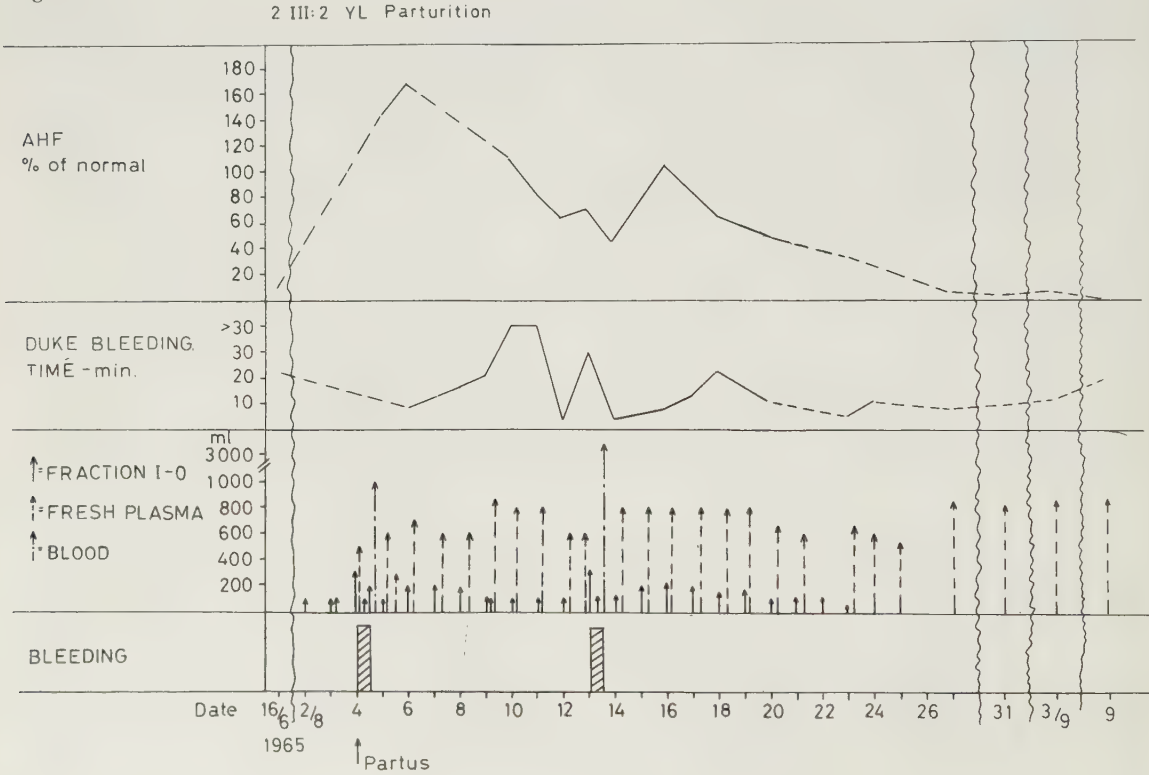


Table 47

Deliveries under protection of F I - 0 and/or fresh plasma

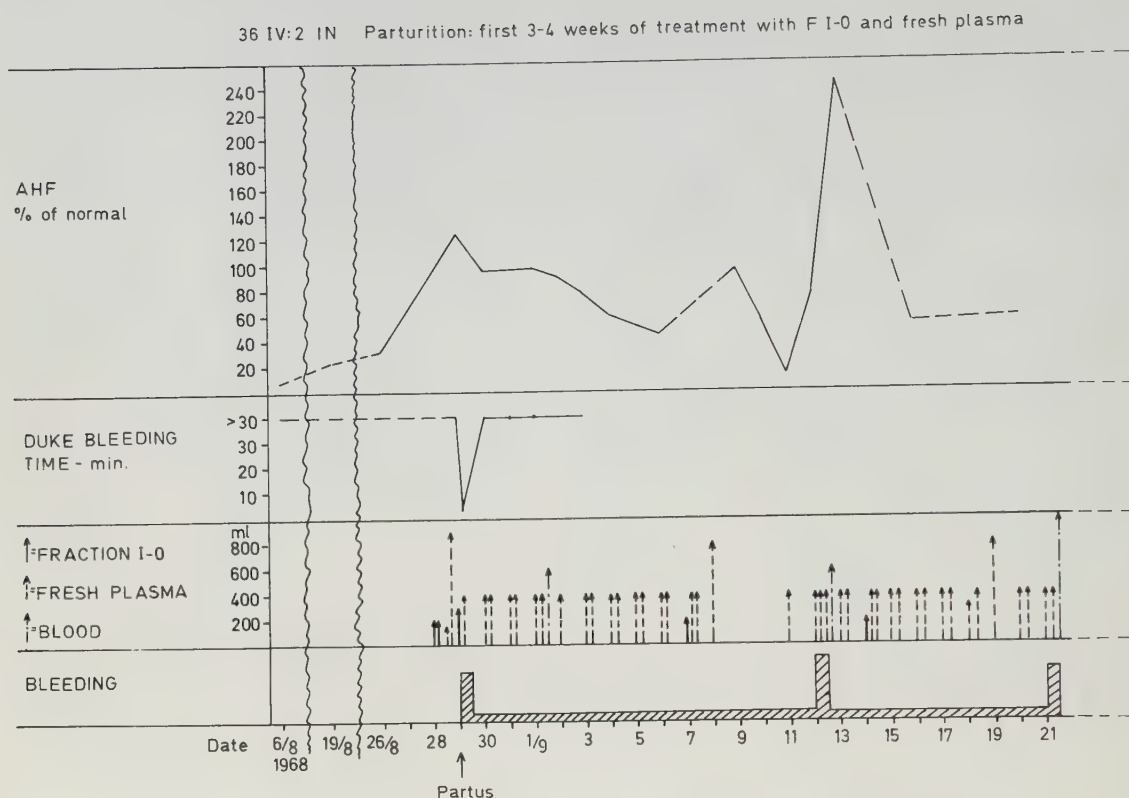
Patient	Age years	AHF % at the		Bleeding time Duke: minutes at the		Given			Dur of treatm. days	Comments
		before pregn.	end of pregn.	before pregn.	at the end of pregn.	before delivery	after delivery			
2 III:2 YL 24	24	3-4	10	>30	22	F I-0 x 100 ml	Plasma x 400 ml	F I-0 x 100 ml	Plasma x 400 ml	Blood x 450 ml
						6		35	45	11
										31
22 II:2 ID 22	22	15-39	61	27-29 (Ivy)	13-14 (Ivy)	2	6	6	28	
										31
26 III:2 EF 26	26	17		>30	11-18	2		0+6	2+1	0+1,5
										3+7
36 IV:2 IN 20	20	2	4.8	>30	>30	4	2,5	27	60	8
										65
77 II:7 HR 24	24	52.5		>30 (Ivy)	16 (Ivy)	1		1		2

Delivery by vacuum extr. Primary retention of placenta. Blood loss at parturition 1,500 ml. Profuse bleeding again 9 days later. Patient received 3,500 ml blood. Bleeding time during treatment often much prolonged.

Delivery uncomplicated. - 3-4 weeks after parturition fairly profuse vaginal bleeding, for which patient received further treatment with F I-0, fresh plasma and fresh blood. Curettage produced fragments of the decidua, after which bleeding ceased.

Vacuum extr. Bleeding at parturition 900 ml. During the following weeks continued menstruation-like bleeding and exacerbations with profuse bleeding 26 and 44 days after parturition. Bleeding time but little affected by the treatment.

Fig. 9



36 IV:2 IN was delivered by vacuum extraction under protection of F I-O and fresh plasma (Fig. 9). The blood loss at delivery was moderate and was estimated at 900 ml. The patient afterwards received prophylaxis with fresh plasma alone: 800–1,000 ml a day. The AHF-level was satisfactory (44–95%), but the bleeding time according to Duke was repeatedly prolonged (more than 30 minutes). For more than one month blood obstinately oozed from the vagina and on three occasions the bleeding exacerbated, the last time 44 days after parturition. On these occasions the patient was given extra doses of F I-O. After the last exacerbation the patient received F I-O daily, and the bleedings stopped.

Patient 26 III:2 EF had severe von Willebrand's disease, but the mean AHF before pregnancy (17%) was not so low as in the previous patients. Delivery, which was performed under protection of all together 200 ml F I-O and 1,000 ml fresh plasma, was not complicated by abnormal bleeding. But three weeks later she began to bleed from the vagina and was therefore given F I-O and fresh plasma as well as 650

ml fresh blood. Curettage produced fragments of the decidua, after which bleeding ceased.

As for the remaining two patients (including one with severe von Willebrand's disease) who had been delivered under protection of F I-O and/or fresh plasma delivery was not complicated by bleeding.

Of this group of 5 patients, bleeding complications post partum thus occurred in three despite prophylaxis and was most pronounced in those two with the most severe form of the disease. The bleedings could, however, partly be explained by obstetric complications not related to the haemorrhagic disease. The treatment also proved quantitatively insufficient to prevent blood loss during the long time of increased bleeding risk in the puerperium.

Treatment of acute bleedings with F I-O and fresh plasma

In 33 of our patients F I-O and/or fresh plasma was given in the treatment of acute bleeding episodes

(see Table 48). 14 patients, mainly those who had the severe form of the disease, were treated on repeated occasions and for various sorts of bleeding symptoms.

The results of treatment were generally good, and in most cases bleeding was soon controlled,

Sometimes, however, the haemorrhage was refractory and required prolonged and intense therapy (Table 48). The dominating form of bleeding in these cases was gastro-intestinal haemorrhage, which has proved to be the most serious form of spontaneous bleeding in Swedish patients with von Willebrand's disease (see page 118). It is a type of bleeding, which carries a considerable risk also in patients without haemorrhagic disease. I V:5 BT had a gastric polyp that caused severe prolonged bleeding. Treatment was given at her local hospital, and the bleeding did not stop until after administration of numerous doses of F I-O. II II:1 GB seems to have a form of chronic haemorrhagic gastritis. F I-O controlled gastric bleeding but exacerbations recurred at close intervals and in recent years they have been disabling. One patient with mild von Willebrand's disease (34 III:3 IL) died at his local hospital from acute profuse gastric bleeding. The bleeding could be temporarily controlled by 300 ml of F I-O but the patient died before further F I-O could be obtained.

Bleeding in the floor of mouth in one patient (16 III:1 AKZ) spread down towards the larynx and threatened to choke the patient. The condition could not be controlled by fresh plasma. F I-O had here a favourable effect and the bleeding ceased within one day.

Finally, 73 II:5 SE was referred for treatment a few weeks after hysterectomy because after operation she had prolonged and life-threatening vaginal bleeding. She had received all together 12 blood transfusions at the operation and postoperatively von Willebrand's disease was suspected and the patient was given large volumes of fresh plasma and fresh blood as well as several doses of F I-O. But the effect was unsatisfactory and bleeding did not stop until after repeated surgical operations including ligature around the internal iliac artery and re-suture of the top of the vagina.

Effect of treatment with Fraction I—O and/or fresh plasma on AHF-level, bleeding time and platelet adhesiveness

The effect of treatment with F I-O or fresh plasma on the AHF-level, bleeding time and platelet adhesiveness has been studied extensively by various authors.

Nearly all of them have confirmed the observation by Nilsson, Blombäck and co-workers (page 8) that both F I-O and fresh plasma produce an elevation of the AHF-level more than could be expected from the amount of F I-O given and for a longer time than such treatment does in haemophiliacs (Cornu et al. 1961 and 1963, Biggs & Mathews 1963, van Creveld et al. 1963, Fantl & Sawers 1963, Castaldi et al. 1967, Dana 1967 and others).

As for the bleeding time, such treatment has often resulted in normalisation of the values (Achenbach et al. 1959, Weiss 1962 and van Creveld et al. 1963). Many investigators have, however, obtained less certain and more varying results (Spurling & Sachs 1959, Cornu et al. 1961 and 1963, McMillan et al. 1961, Biggs & Matthews 1963, Bowie et al. 1967, Dana 1967 and H. Perkins 1967). Caen, Larrieu and Meyer (1969) claim that the effect on the bleeding time is brief: rarely more than 4 hours. This has also been found to be the case during treatment with cryoprecipitate (H. Perkins: discussion at Medical staff conference. Calif. Med. 1969). Some authors (Meili, Straub & Frick 1969, Komp, Nolan & Carpenter 1970), however, found cryoprecipitate to have a stronger and more prolonged effect on the bleeding time than fresh plasma or Fraction I. — The bleeding time by the technique of Ivy was usually much less affected by treatment with plasma and plasma fractions than the bleeding time according to Duke (Borchgrevink 1963, Cornu et al. 1963, Barrow & Graham 1964, Lemoyne & Larrieu 1967 and Meyer et al. 1969).

Platelet adhesiveness after administration of F I-O or fresh plasma has been examined with Borchgrevink's method (Weiss 1962, Lemoyne & Larrieu 1967) and with Salzman's method and modifications of Salzman's method (Salzman 1963 and 1967, Strauss & Bloom 1965, Meyer et al. 1969, H. Perkins 1969 and Hellem 1970). Some authors (Salzman 1963 and 1967, Lemoyne & Larrieu 1967, Meyer et al. 1969 and Hellem 1970) have found F I-O or plasma to normalise reduced platelet adhesiveness, while others (Weiss 1962, Strauss & Bloom 1965 and H. Perkins 1969) have found such treatment to have no effect on platelet adhesiveness.

The clinical effect on the bleeding tendency at operations was more related to the AHF-level than to the bleeding time according to Larriet et al. (1968) and Rizza and Biggs (1969). The opposite view was held by Komp, Nolan and Carpenter (1970) and by Meili, Straub and Frick (1971)

Table 48

Acute bleedings treated with F I-0 and/or fresh plasma

Patient	Age years	Type	Symptom	F I-0 x100 ml	Given Plasma x400 ml	Blood x450 ml	Dur. of treatm. days	Comments
12 IV:2 KPA	9	Sv	Nose bleeding	2		3		
16 III:1 AKZ	16	Sv	Nose bleeding	17		1	15	Simultaneous ovarian bleeding
19 AKX	19	Sv	"	1			1	
22 II:1 ID	24	Sv	Nose bleeding	10	10	10	9	Bleeding after stopping treatment with "p-pills"
30 III:2 AW	8	Mi	Nose bleeding	2			4	
42 IV:62 PS		Mi	Nose bleeding	1			1	
61 III:1 EK	7	Mi	Nose bleeding		0,5		1	Cauterised with chromic acid
90 III:1 ML	1	Sv	Nose bleeding	0,5			1	
ML	1	Sv	"	0,5			1	
ML	2	Sv	"	1			1	
ML	3	Sv	"	0,5		1	1	
92 III:1 AM	1	Sv	Nose bleeding		0,5	0,5	1	Cauterised with chromic acid
AM	1	Sv	"				1	
3 III:1 MH	18	Sv	Gingival bleeding		+			
MH	21	Sv	"		+			
6 IV:2 RF	6	Sv	Bleeding at tooth shedding	1			1	
40 III:3 AMW	7	Sv	Bleeding at tooth shedding	1			1	
AMW	11	Sv	"		1		1	
AMW	11	Sv	"	1	1		2	
AMW	11	Sv	"	1	1		3	
AMW	11	Sv	"		1,5	1	3	
6 IV:2 RF	2	Sv	Traumatic oral bleeding		0,5	2	3	
90 III:1 ML	1	Sv	Traumatic oral bleeding	0,5			1	
100 III:4 AS	4	Mi	Traumatic oral bleeding	3			11	
103 II:3 AW	7	Sv	Traumatic oral bleeding	1			1	Pat. received also €-ACA
2 III:3 GL	7	Sv	Tonsillar bleeding	1,5			1	
9 III:1 ES	29	Sv	Tonsillar bleeding	2	3	2	1	
23 III:12 KW	8	Sv	Tonsillar bleeding	2		2	1	
KW	10	Sv	"			1	1	
40 III:3 AMW	10	Sv	Tonsillar bleeding	1			1	
6 IV:2 RF	1	Sv	Bleeding after venous puncture	1			1	
92 III:1 AM	1	Sv	Bleeding after arterial puncture	1,5				
6 IV:2 RF	13	Sv	Subcutaneous bleeding		3,5		5	
40 III:3 AMW	8	Sv	Subcutaneous bleeding	1	0,5		1 + 1	
16 III:1 AKZ	12	Sv	Bleeding in floor of mouth	10			10	
6 IV:2 RF	12	Sv	Intramuscular bleeding	2			4	

Table 48 (continued)

Acute bleedings treated with F I-0 and/or fresh plasma

Patient	Age years	Type	Symptom	F I-0 x100 ml	Given Plasma x400 ml	Blood x450 ml	Dur. of treatm. days	Comments
63 II:5	86	Mi	Intramuscular bleeding		10		10	
42 IV:46	10	Mi	Traumatic bleeding	2			3	
48 III:1	7	Sv	Traumatic bleeding	2		0.5	2	
1 V:5	28	Sv	Gastrointestinal bleeding	31		23	30	Bleeding from gastric polyp
9 III:1	23	Sv	Gastrointestinal bleeding		3	2		
10 III:1	32	Sv	Gastrointestinal bleeding	5	2	6	4	
	34	Sv	Gastrointestinal bleeding	19		1	15	
	36	Sv	"	4			4	
11 II:1	51-56	Sv	Gastrointestinal bleeding	>300		numerous		More than 100 periods of treatment
34 III:2	45	Mi	Gastrointestinal bleeding	3		several	3	Patient died before further F I-0 could be obtained
50 I:2	41	Mi	Gastrointestinal bleeding	2		2	2	
89 II:2	81	Mi	Gastrointestinal bleeding	2	10	2		Hepatitis afterwards
7 III:1	25	Sv	Haematuria		8		7	
13 III:2	23	Sv	Haematuria	2	3		1	
	23	Sv	"		1	1	2	
	23	Sv	"		1		1	
	24	Sv	"		7		5	
	24	Sv	"		7		7	
	26	Sv	"		3		2	
	12	Sv	Menorrhagia	1		2	2	
2 III:3	14	Sv	"	1		3		
	15	Sv	"	2		3		
16 III:1	12	Sv	Menorrhagia		4	2	8	Bleeding stopped after treatment with progesterone
23 III:12	13	Sv	Menorrhagia	1		2	1	Pat. received also €-ACA
42 III:19	50	Mi	Menorrhagia	2			1	
54 III:2	12	Mi	Menorrhagia		1		1	
7 III:1	14	Sv	Ovarian bleeding	1			1	
10 III:1	28	Sv	Ovarian bleeding	2			3	
	35	Sv	"	8		3	8	Pat. received also €-ACA
16 III:1	16	Sv	Ovarian bleeding	17			15	Simultaneous nose-bleeding
6 IV:2	8	Sv	Joint bleeding	2	2		6	
6 IV:2	8	Sv	Joint bleeding	2	2		6	
	12	Sv	"		1		1	
8 II:1	33	Sv	Joint bleeding		1		1	
	33	Sv	"		1		1	
	34	Sv	"		1		1	
	34	Sv	"		1		1	

Table 48 (continued)

Acute bleedings treated with F I-0 and/or fresh plasma

Patient	Age years	Type	Symptom	F I-0 x100 ml	Given Plasma x400 ml	Blood x450 ml	Dur. of treatm. days	Comments
8 II:1	34	Sv	Joint bleeding		1		1	
	34	Sv	" "		1		1	
	34	RB	" "		4			
	34	Sv	" "				1	
	35	Sv	" "	1				
	35	Sv	" "		2,5		1	
9 III:1	20	Sv	Joint bleeding		1		1	
	21	Sv	" "		1		1	
	21	Sv	" "		2		1	
	22	Sv	" "		1		1	
	23	Sv	" "		1		1	
	23	Sv	" "		1		1	
	23	Sv	" "		1		1	
	23	Sv	" "		2		1	
	23	Sv	Joint bleeding		0,5		1	
	3	Sv	Joint bleeding		1		1	
	7	Sv	" "		1		1	
	8	Sv	" "		1		1	
48 III:1	8	Sv	" "		1		1	
	8	Sv	" "		2		2	
	8	Sv	" "		3		4	
	5	Sv	Joint bleeding		2		3	
	7	Sv	" "		1		1	
	7	Sv	" "		1		1	
100 III:4	4	Mi	Joint bleeding	1			1	
	3	Mi	Joint bleeding		0,25		1	
	28	Mi	Eye bleeding		5		5	
	1	Sv	Retropitoneal bleeding?	1			1	
	41	Mi	Postextraction haemorrhage	1			1	
	5	Mi	Postextraction haemorrhage	15			11	
	38	Mi	Bleeding after hysterectomy	52,5	30	50	22 ¹⁾	
	49	Mi	Bleeding after hysterectomy	2	9	9	45 ¹⁾	
								Hepatitis afterwards
								Hepatitis afterwards

¹⁾ Duration from the beginning of treatment with plasma.

Fig. 10

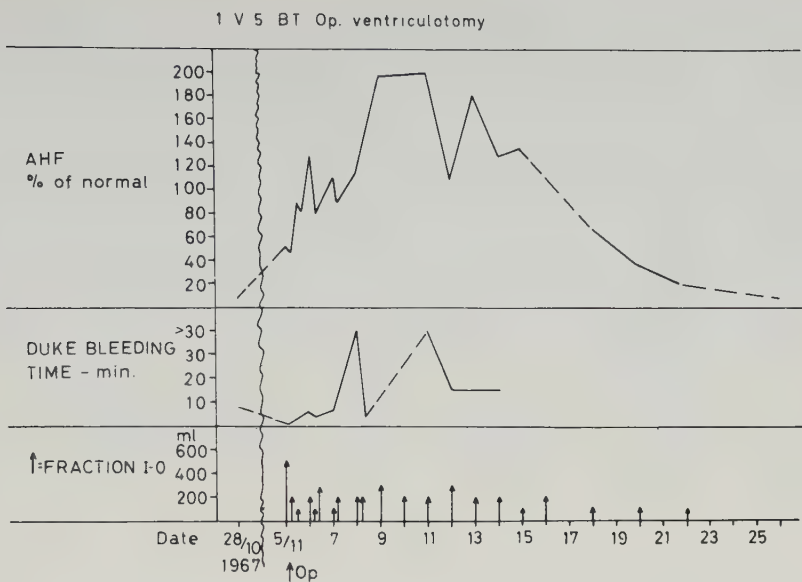


Fig. 11

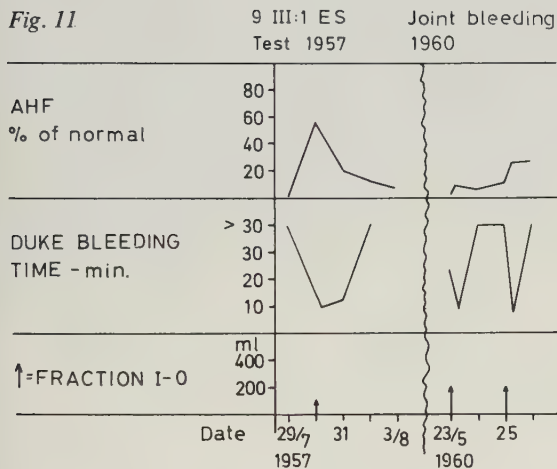
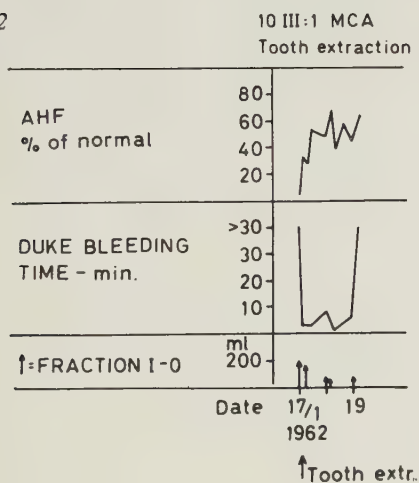


Fig. 12



Present series

In Swedish patients given F I-O or fresh plasma the AHF-level and the bleeding time were often followed with repeated determinations. The results are illustrated by fig. 6–18 (page 121–135).

With but few exceptions such treatment raised the AHF in the patient's blood. The highest values were generally obtained 6–8 hours after infusion, and the AHF-level was then higher than could be expected from the amount of AHF given. The increase was larger than that obtained on infusion of a corresponding amount to patients with haemophilia A. The effect of a dose usually lasted for 24–28 hours. When the doses were given at 24 hour or shorter intervals, they generally produced a stepped elevation of the AHF-level, and sometimes the AHF-values exceeded 100% even in patients with previously very low values

Fig. 13

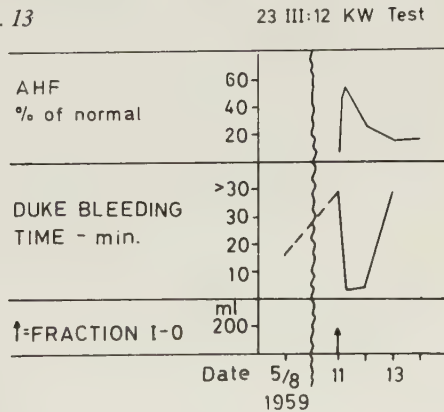


Fig. 14

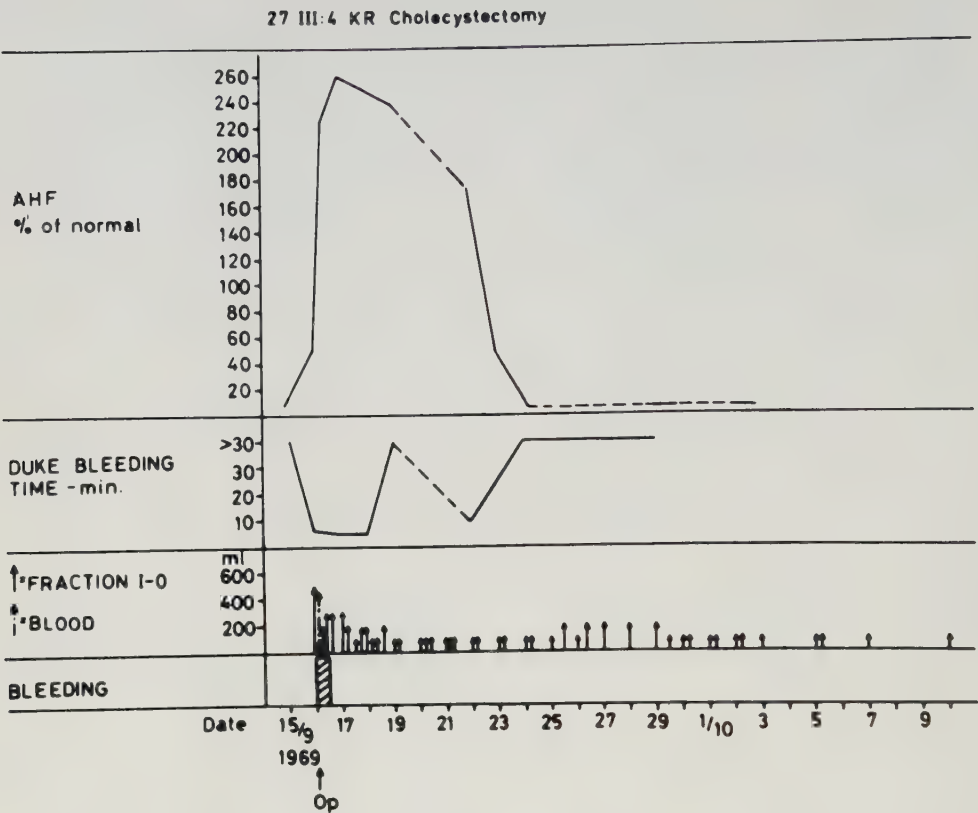


Fig. 15

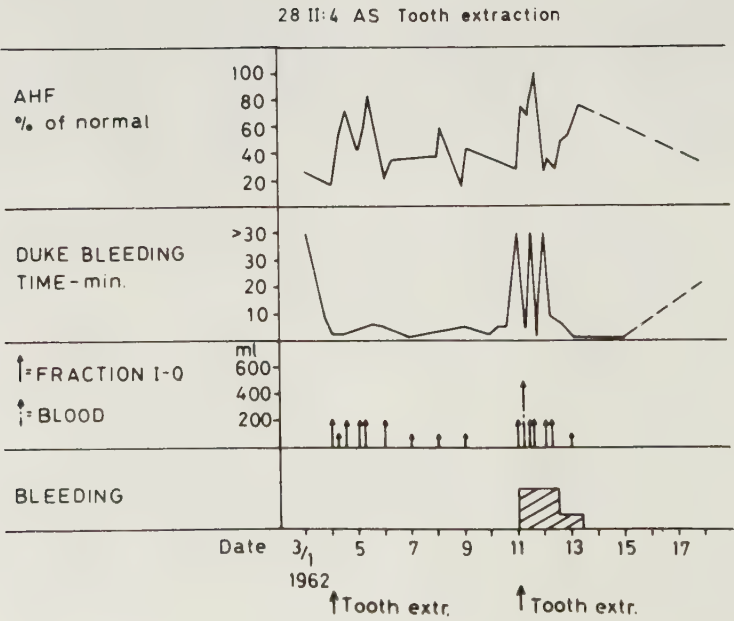
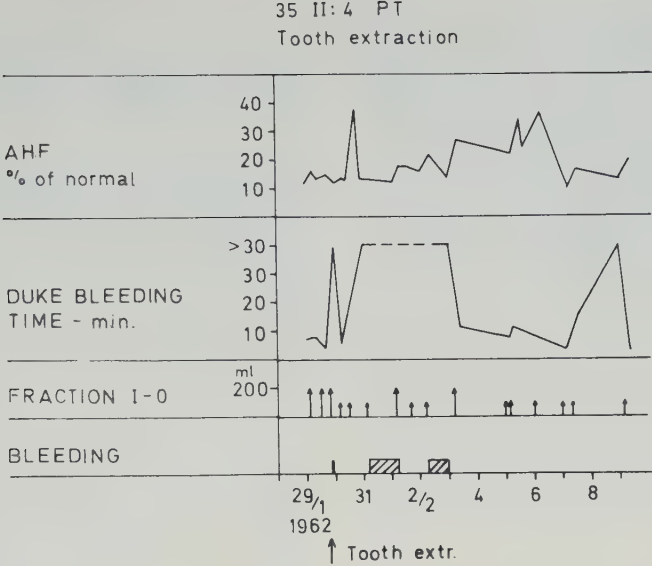


Fig. 16



(Figs 7, 10 and 14). After repeated administration of F I-0 for a long period the effect sometimes became less certain and brief (Figs. 6, 8 and 14). In one of these cases (Fig. 6, 16 III:1 AKZ) examination has revealed signs of a circulating anticoagulant.

An unsatisfying response by AHF from the very beginning was seen in 35 II:5 PT (Fig. 16) and was found to be due to an anticoagulant. In some patients (28 II:4 AS Fig. 15 and 33 III:2 AR) the response was

poor when F I-0 had been prepared in large batches with freshly frozen plasma as a basic material and when the fractions had been sterile filtered before use (see page 12 Material and methods).

The effect of F I-0 and fresh plasma on Duke's bleeding time was good in most cases but generally shorter than the effect on the AHF-level (see page 7). When the doses used were too small and given only at intervals of more than 12 hours the bleeding time in patients with severe von Willebrand's disease often was abnormally long in spite of treatment (Figs. 7, 8, 9, 14 and 15). With the commercially available preparations of F I-0 in recent years the effect on the bleeding time has sometimes been less satisfactory (45 III:1 RO, 103 II:3 AW, Fig. 18).

Fig. 17

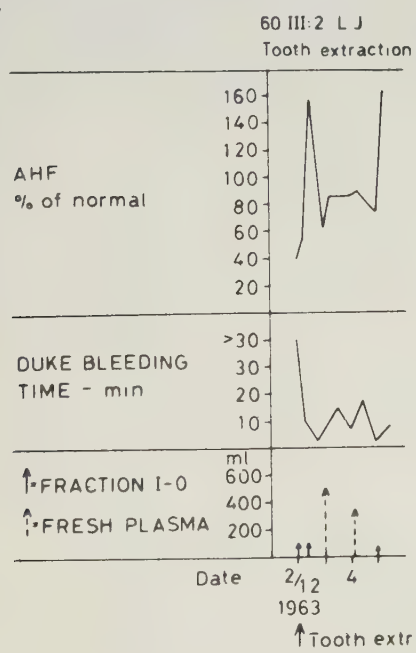
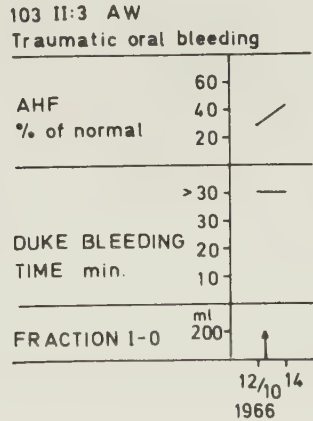


Fig. 18



Side effects

Ivy bleeding time was barely affected by the treatment. This may be due at least partly to the fact that the bleeding time was not measured for more than 30 minutes and that a reduction of a markedly prolonged bleeding time might have not been noticed.

The results of treatment on the patient's bleeding tendency usually varied with the effect of treatment on the AHF-level and Duke bleeding time. When the bleeding time according to Duke was markedly prolonged, profuse bleeding sometimes occurred even when the AHF-level was high (Figs. 7, 8 and 9).

A normal bleeding time according to Duke usually reflected good control of the bleeding tendency, also at major operations even when the bleeding time according to Ivy was still prolonged.

The profuse bleeding that occasionally occurred during treatment usually occurred when treatment was tentatively withdrawn or when F I-O or plasma was given at longer intervals.

In some cases determinations were made of platelet adhesiveness according to Salzman before and after administration of F I—O. The results are listed in Table 49.

The most serious and most common complication of treatment with F I-O and plasma was serum hepatitis. It occurred in 6 cases: 8 II:1 RB, 13 III:2 SE, 16 III:1 AKZ, 48 III:1 BH, 50 I:2 MA and 89 II:2 HN. It was most severe in 50 I:2 MA in whom the bilirubin rose to 5.1 mg/100 ml, GPT to 2,000 U and Thymol ext. to max 0.64 (normal <0.10). Liver function gradually became normal within some months. — In the other cases the symptoms of hepatitis were relatively mild and brief.

Signs of a circulating anticoagulant were seen in two patients: 16 III:1 AKZ and 35 II:4 PT. The former had previously been repeatedly treated with F I-O and fresh plasma. In 35 II:4 PT, on the other hand, the very first dose of F I-O had a poor effect on the AHF-level. On electrophoresis a band was found in the β_2 -globulin fraction. A connection between the band and the anti-AHF is possible. Later the patient fell ill with myeloma.

In three cases (36 IV:2 IN, 38 IV:4 KS and 75 II:1 BT) treatment with fresh plasma was followed by aller-

Table 49

Platelet adhesiveness according to Salzman before and after administration of F I—O.

Patient	Platelet-adhesiveness %		Bleeding time according to Duke		Time after infusion of F I-O ¹⁾
	before infusion of F I-O ¹⁾	after infusion of F I-O ¹⁾	before infusion of F I-O ¹⁾	after infusion of F I-O ¹⁾	
1V:5 BT	7				
	10	11,5	> 30	3	
10 III:1 MCA	0	8	> 30	8	20'
11 II:1 GB	3	6	> 30		0
	3	3		8	
	3	8		5'30"	
	3	3		2	
12 III:2 KPA	6	2	20	11	20'
		4			20'
		7			20'
		2		4'30"	20'
103 I:1 WW	0	24			
II:3 AW	20	22			
27 IV:1 KR	17	10			24 hr's

¹⁾ dose 100—500 ml.

Treatment thus had no regular or particular effect on platelet adhesiveness. No normalisation occurred parallel to the bleeding time according to Duke.

gic urticaria and oedema. In 38 IV:4 KS there was also a swelling of the throat and in 75 II:1 BT hoarseness. But in none of the patients were the symptoms serious.

TREATMENT WITH ϵ -ACA and AMCA

Therapy and prophylaxis with ϵ -ACA have been used by some investigators in recent years. Good results have been reported by Henrion and Cornu (1964). Bowes (1969) and van Creveld and Schellekens (1969), on the other hand, found such drugs to have no effect on the bleeding tendency.

Present series

Data on therapy or prophylaxis with ϵ -ACA or AMCA are available for 20 patients with von Willebrand's disease in Sweden. ϵ -ACA has been given i.v. in a dose of 12-45 g/24 hours or orally in a dose of 3 g x 4-6. AMCA has been given in a dose of 1-4 g a day. The doses have been varied according to the patient's weight, the extent of operations, and the severity of the bleedings for which treatment was started.

It is difficult to assess the effect of medication because, as a rule, the patients had also received other treatment. One patient, 8 II:1 RB, with a strong predisposition to joint bleedings, however, reported a considerable improvement during almost 2 years' continuous treatment with AMCA without any simultaneous therapy. During this period he has not had any recurrence of joint bleedings. At 34 years (1969) 13 III:2 SE was treated with AMCA because of obstinate nose-bleeding. The bleeding stopped after

6 hours. The patient previously had frequently recurrent bleeding from the urinary tract. He has since successfully used ϵ -ACA or AMCA as soon as he has noticed signs of such bleeding and has not required hospitalisation. Some patients have tried daily treatment with AMCA at or before expected menstruation but have been unable to continue such treatment owing to side effects, especially in the form of abdominal pain and diarrhoea.

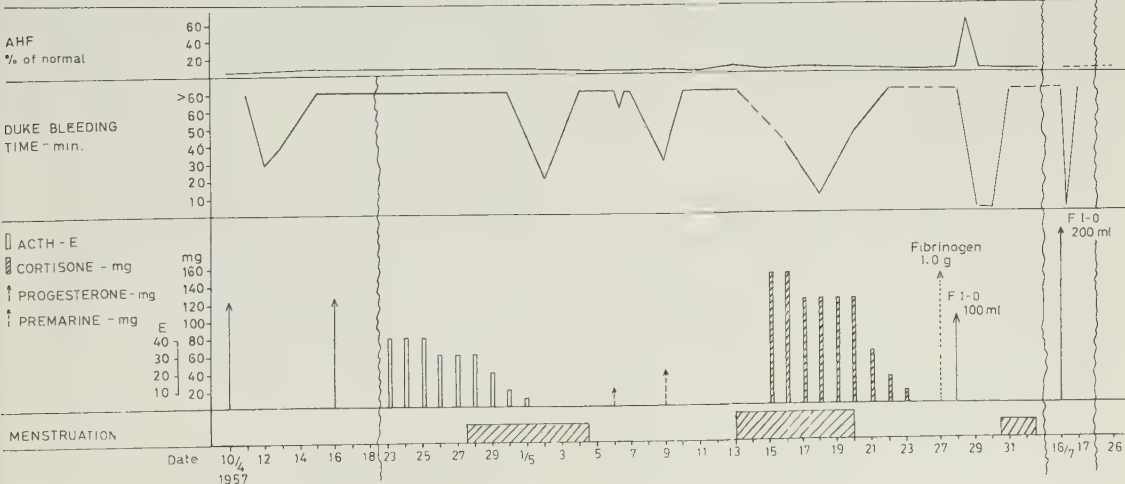
TREATMENT WITH CORTICOSTEROIDS AND ACTH

Cortisone has been recommended in the treatment of conditions with a normal platelet count and prolonged bleeding time, particularly by B. Jacobsson (1953 and 1957). In our series the effect of ACTH and cortisone was tried in 7 III:1 MA, who received treatment before and in association with profuse menstrual flow (Fig. 19). After treatment with ACTH and during treatment with cortisone the bleeding time transiently became shorter but not normal. During cortisone treatment the bleeding time again became prolonged before treatment was withdrawn. Therapy had no convincing effect on the menstrual flow.

TREATMENT WITH SEX HORMONES

Various sorts of hormone preparations have been tried in the treatment of menorrhagia in von Willebrand's disease during the last decades (Achenbach 1960, Carré et al. 1961, Barrow & Graham 1964:a, Bonechi & Pasero 1964, Akman et al. 1965, Özoylu & Corbacioglu 1967 a and b, van Creveld & Shellekens 1969 and others).

Fig. 19 7 III:1 MA The effect of various forms of therapy



In the 1960s contraceptives have become available in which oestrogenic and gestagenic components have been given usually in so called combined preparations. These preparations have been found to have a considerable depressive effect on menorrhagia (Carré et al. 1961, Henrion & Cornu 1964, Özsoylu & Corbacioglu 1967, a and b, Walker & Dormandy 1968). The effect can probably be ascribed above all to the local effect of the hormones on the endometrium. But their possible effect on the coagulation mechanism and platelet adhesiveness has also been discussed and compared with the effect of pregnancy during which the AHF is also normally elevated.

Egeberg and Owren (1963) found that treatment with Enavid® (Searle) in a standard contraceptive dose to 4 healthy women caused an increase of the AHF, which developed during the first and second week of treatment, while the values showed a tendency to return to the original levels soon after discontinuation of treatment.

Other investigators have not found oral contraceptives in ordinary doses to have any definite effect on the AHF (Rutherford et al. 1964, Brakman, Albrechtsen & Astrup 1967, Nilsson & Kullander 1967). However, Nilsson and Kullander (1967) found the use of Anovlar® (Schering AG) in 4 times the ordinary dose for $2\frac{1}{2}$ –6 months to raise the AHF by roughly 100%.

Özsoylu and Corbacioglu (1967 a and b) gave contraceptive pills to patients with von Willebrand's disease, even to men, and then followed the bleeding status with laboratory tests. They found the AHF to raise but not until treatment had been continued for 2–6 months and then not to reach a maximum until after 5–11 months. The male patients had by then developed gynaecomastia and in a few cases also behavioural disturbances. Platelet adhesiveness had not been affected by the hormone therapy and the bleeding time had not noticeably improved.

Present series

One of our patients, a girl, 7 III:1 MA, was successfully treated in the middle of the 1950s with progesterone because of severe puberal menorrhage. Menorrhagia did not recur after withdrawal of the preparation after it had been used for one year. Progesterone therapy has since been used for similar symptoms in 2 III:3 GL and 16 III:1 AKZ. The former improved considerably, while the effect of treatment on the latter was unsatisfactory. In this patient

progesterone was therefore replaced by a testosterone preparation. After three years' treatment the drug had had a strong virilising effect. Treatment was therefore discontinued and the patient was subjected to hysterectomy instead.

In recent years contraceptives with oestrogenic and gestagenic components, "p-pills" have been given to several Swedish patients because of menorrhagia, and the clinical results have been good. It appeared to be of interest to study the effect also on some of our patients regarding the AHF, bleeding time according to Duke and Ivy and platelet adhesiveness.

Four women with von Willebrand's disease of varying severity received pills Conlunette (Noretisteron 1 mg + Mestranol 0,1 mg) in a standard dose, *i.e.* one pill a day for three weeks followed by one week's pause. Treatment was continued for 3–5 months. The patients were examined before treatment, during treatment, during prescribed pauses in treatment and at least three weeks after the end of treatment. Three of the patients (38 IV:4 KS, 9 III:1 ES and 22 II:1 ID) had previously used similar "p-pills" and one of them (9 III:1 ES) did not wish to stop medication when the program had been concluded. The results are given in Table 50.

Treatment with "p-pills" thus had no noticeable effect on the values studied. The only remarkable finding was that all of the 4 patients studied had a lower mean AHF during the pauses in treatment than before, during and after treatment. Two, who had before treatment only had moderately increased bleeding time according to Duke showed a possible tendency to more prolonged bleeding time during the pauses.

During treatment with "p-pills" all the patients were free from menorrhagia, which had previously caused more or less severe symptoms. They also all reported that they felt better even regarding other bleeding symptoms which had before treatment often been troublesome such as tendency to nose-bleeding and bruising: 9 III:1 ES, who had formerly been regularly using "p-pills" stopped taking the pills for about one month before the present investigation. She had previously had troubles of joint bleeding, and during the pause symptoms of bleeding in the elbow, knee and foot joint occurred. 22 II:1 ID one month after she had stopped using the pills had severe nose-bleeding which resulted in shock necessitating several blood transfusions.

These bleeding symptoms thus occurred after discon-

Table 50

AHF, bleeding time according to Duke and Ivy and platelet adhesiveness according to Salzman before, during and after treatment with "p-pills".

Patient	AHF (%)			Bleeding time according to Duke (minutes)			Bleeding time according to Ivy (minutes)			Platelet adhesiveness according to Salzman (%)		
	Before treatment	During treatment	Pause	After treatment	Before treatment	During treatment	Pause	After treatment	Before treatment	During treatment	Pause	After treatment
9 III: 1 ES	2.5	3.7	1.5		>30	>30	>30	>30	14	0	28	27
	2.5	2.1			>30	>30	>30	>30		6	3	
22 II: 1 ID	32	24	11		>30	>30	>30	>30	0	17	22	
	26	20	9		>30	>30	>30	>30	18	12		
38 IV: 4 KS	25	25	18	21.3	8 7	9 16		>30	19	30	9	1
	29		7.3		9 13	15 1	>30	>30	10	14	2	
42 III:26 EN	43	35	37	32	9 9	3 4	11 13	>30	16	6	24	18
	30		10		2 5	3 9		>30		0	31	

tinuation of treatment with "p-pills" for more than a week, which is prescribed for ordinary contraceptive purposes. During the one-week pauses, on the other hand, the patients noticed no increased bleeding tendency.

The investigation could unfortunately be carried out only on 4 patients. The results of this investigation thus showed a general reduction of the bleeding

symptoms during the use of "p-pills" and not only of menorrhagia but also of bleedings in other organs. No corresponding normalisation of the results of laboratory tests were, however, obtained.

Schedule of treatment

A schedule of treatment of von Willebrand's disease with F I-0 and fresh plasma is given below.

Table 51

Schedule of treatment of von Willebrand's disease with AHF (F I-0) and fresh plasma (After Nilsson 1971)

	Desired lab. values for		Duration of treatment	Severe cases		Mild cases	
	AHF	Duke min.		Dose AHF /24 hrs (units ¹)/kg)	Therapeutic substance	Dose AHF /24 hrs (units ¹)/kg)	Therapeutic substance
Major operations							
Tonsillectomy	40-70%	≤ 5	2-3 weeks	Day 1-2: 20-40	1) AHF-concentrate, Kabi,	Day 1-2: 15-30	1) AHF-concentrate, Kabi
Gastrectomy	during op. and first few days after op.			Day 3-8: 10-20	possibly combined with plasma	Day 3-8: 5-15	2) Cryoprecipitate
Cholecystectomy	40% till about 7th postop. day; afterwards 10-15% until healed			From day 9: 5-10	2) Cryoprecipitate, possibly combined with plasma	From day 9: 5	3) Plasma
Hysterectomy							
Minor operations							
Tooth extraction	20-50% during op. and afterwards about 15% for 6-8 days	≤ 5	6-8 days	Day 1: 15-20	1) AHF-concentrate, Kabi,	Day 1: 5-15	1) AHF-concentrate,
Appendectomy				Day 2-8: 5-10	possibly combined with plasma	Day 2-8: 5	2) Cryoprecipitate
Operation for hernia					2) Cryoprecipitate, possibly combined with plasma		3) Plasma
					3) Plasma		
Deliveries	as for major operations	≤ 5	2-4 weeks	as for major operations		possibly as for minor operations	
Severe bleeding conditions							
Gastro-intestinal bleeding	20-50%	≤ 5	about 7 days	15-20	1) AHF-concentrate, Kabi, possibly combined with plasma	5-15	1) AHF-concentrate, Kabi
Severe menorrhagia					2) Cryoprecipitate, possibly combined with plasma		2) Cryoprecipitate
Head injury					3) Plasma		3) Plasma
Intracranial haemorrhage							
Postop. bleeding							
Minor bleeding episodes							
Superficial injuries	15-20%	≤ 10	2-5 days	5-10	1) AHF-concentrate, Kabi	possibly 5	1) Possibly plasma
Nose-bleeding					2) Cryoprecipitate		
Haematuria					3) Plasma		

At operation also Epsikapron® or Cyklokapron® may be given with advantage

¹) 1 unit the AHF-content of 1 ml normal plasma

GENERAL DISCUSSION

INTRODUCTION

In the middle and end of the 1950s Nilsson, Blombäck and co-workers published the results of investigations of von Willebrand's disease in Sweden and its treatment with fresh plasma and Fraction I-O. The discovery of a plasma factor, influencing the production of AHF and normalising the bleeding time had a decisive effect on later research in this field.

Since that time the coagulation laboratories in Malmö and Stockholm have been especially interested in von Willebrand's disease and its treatment. Patients in Sweden with suspected von Willebrand's disease are mostly referred to one or the other of these laboratories for examination, and a joint register has been set up of all known cases of von Willebrand's disease in the country. This register also includes families in which the disease was first diagnosed at the coagulation laboratory in Gothenburg. The treatment of all patients known to have the bleeding disease, has, as a rule, been performed under the supervision of either Professor I.M. Nilsson, Malmö or Docent M. Blombäck, Stockholm.

By Jan. 1, 1968, in all, 84 families with a firm diagnosis of von Willebrand's disease had been entered in the above mentioned register. The probands and other patients with more pronounced bleeding symptoms have been investigated with careful inquiry into their histories and a detailed analysis of their bleeding and coagulation status. In addition, a large number of relatives of the patients have been examined anamnestically and with the most important laboratory tests for von Willebrand's disease, *viz.* determination of AHF and of the bleeding time according to Duke and to Ivy. In about half of all cases determinations have also been made of platelet adhesiveness according to Salzman. As for the relatives who, according to information obtained, had had notable bleeding symptoms but who had not been available for examination, the records had usually been obtained from hospitals where they had been treated.

The purpose of this investigation was to analyse the comprehensive collection of historical, clinical and laboratory data in order to assess the frequency of the disease in the country, its heredity, symptomatology, and prognosis. The investigation was also extended to include diagnostic problems and a brief outline of the

experience hitherto gained with different kinds of treatment.

FREQUENCY

von Willebrand's disease has recently been supposed to be the commonest known hereditary bleeding disease (Quick 1967:a, Aggeler 1969 and J. Jürgens 1969). But so far no investigations have been published on the actual frequency in a defined population.

The present material includes practically all known cases of von Willebrand's disease in Sweden by Jan. 1, 1968. We had then traced 255 patients with a firm diagnosis of von Willebrand's disease. At that time the population of Sweden was about 7.9 millions. This means a frequency of at least 1:32,000. The corresponding figure for haemophilia is, according to Ramgren (1962), 1:15,000 males, *i.e.* barely 1:30,000 of the entire population. It is often difficult to decide whether von Willebrand's disease is present or not, and for 55 persons in the present material the results obtained were intermediate, according to the definition given on page 13. Similar intermediate results have been obtained also for other persons examined because of suspected von Willebrand's disease, but not belonging to any of the families included in this presentation. Furthermore, there are probably several affected persons with mild bleeding manifestations who have not yet been examined. The frequency of concealed mild cases is presumably much higher than in haemophilia. It is therefore probable that von Willebrand's disease is the most common hereditary bleeding disease in Sweden.

Patients with von Willebrand's disease appear to be fairly evenly distributed among the population.

HEREDITY

Most researchers believe the inheritance of the disease to be autosomal dominant (von Willebrand, Jürgens & Dahlberg 1934 and others, See page 82.)

The disease has been found to vary in penetrance and in expressivity (von Willebrand 1931 and others. See page 82).

In several series females have been found to be predominant (von Willebrand 1926 and others. See page 82).

Graham (1959) suggested the possibility of different changes responsible for the tendency to bleeding in von Willebrand's disease to be inherited separately, *e.g.* low AHF-content from one of the parents and prolonged bleeding time from the other.

In our material we were able to show bleeding symptoms in relatives of probands in 59 of 84 families (72 %) (Table 7). Certain signs of the occurrence of the disease in relatives have been seen in a further 15 families.

The investigation has corroborated the general opinion that the disease is inherited as an autosomal dominant.

The estimated penetrance in the investigation of parents was 73–90 %.

The expressivity varied widely, often also within a given family. But with the analysis of variance we have shown that, as for the AHF-content, the expressivity is much more uniform within sibships than between unrelated patients ($p < 0.001$) (Table 9). Affected children also resemble their affected parents in respect of AHF more than unrelated patients. The statistical significance of the X^2 -test was $p < 0.05$.

The number of females among our patients with a firm diagnosis of von Willebrand's disease was larger than the number of males (Table 10). This may be because the disease is often manifested by uterine bleeding. It is of interest, however, to note that among the cases judged as severe mainly from laboratory tests, there were 23 females and only 9 males. This might suggest a stronger expressivity among females than among males. But the figures are not large enough to warrant any conclusions.

Because of Graham's hypothesis, the chapter on heredity includes an analysis of the correlation between values for AHF and bleeding time for both the affected and the unaffected subjects studied (Table 11). We found a close correlation between reduced AHF-content and prolonged bleeding time. This argues against Graham's hypothesis.

We feel that the bleeding time and AHF-level are dependent on a common factor, the von Willebrand-factor. The formation of this factor may in turn be influenced by one or more genes. Certain phenomena or circumstances such as physical and mental stress may then exert a temporary modifying effect on the amount and activity of the factor (page 108–109).

SYMPTOMATOLOGY

The symptomatology of von Willebrand's disease has been described in detail by von Willebrand himself

(von Willebrand 1926 and 1931). But it appears that no serious attempts have been made to calculate the frequency of various symptoms in a larger series of patients with a firm diagnosis. We compared our frequency figures (Table 13) with Buchanan and Leavell's (1956) large compilation of published cases of "pseudohaemophilia", in which most of the patients probably had von Willebrand's disease. The comparison showed a fairly good agreement regarding the occurrence of bleeding from various organs.

The commonest types of bleeding were nose-bleeding, uterine bleeding, ecchymoses and haematoma, and bleeding after tooth extraction.

The haemorrhages that caused the greatest loss of blood are given in a special table (Table 14). Such heavy losses were most commonly found in patients with severe von Willebrand's disease and occurred particularly as postoperative bleeding, meno-metrorrhagia, gastro-intestinal haemorrhage and nose-bleeding.

As for nose-bleeding, we noticed that such bleeding often occurred at, or soon after, other bleeding manifestations. Like Achenbach (1960), we often found that patients had considerable nose-bleeding after surgical operations, even after operations on remote organs, such as the ovaries or the uterus. Such bleeding may have been due to consumption of AHF at and after surgery.

Traumatic bleeding of the lips and oral cavity proved to be a typical symptom of von Willebrand's disease in young children, especially in those with the severe form of the disease.

Traumatic bleeding does not otherwise generally cause a heavy loss of blood in patients with von Willebrand's disease. This may be because cessation of bleeding following severe trauma is more dependent on the coagulation mechanism, which is rarely seriously disturbed in von Willebrand's disease (see page 5). In addition, severe trauma results in the release of tissue thromboplastin. A low AHF-content will therefore be of less importance for the bleeding tendency.

A special group of traumatic haemorrhages are intracranial haemorrhages, and such bleeding proved fatal in two of our patients with the severe form of von Willebrand's disease (Table 16). The patients had a very low AHF-level. In this connection the disease may be compared with haemophilia where intracranial haemorrhages have proved to be the commonest cause of death in recent years (Ramgren 1962, Blattner 1967).

Ecchymoses and haematoma were often the initial symptoms of the bleeding tendency. Petechiae were uncommon.

Menorrhagia was, as a rule, most severe among young girls the first few years after menarche (Table 18). It probably often occurred as anovulatory bleedings, intensified by the bleeding disease (see van Creveld and Schellekens 1969). One patient died and three were subjected to hysterectomy or roentgen castration before the age of 16 years. Some patients had anaemising menstruation throughout the age of reproduction.

Deliveries of women in the present material with the severe form of the disease occurred only under cover of Fraction I-O and fresh plasma. In the mild cases of von Willebrand's disease profuse post partum bleeding, requiring blood transfusions occurred in 8.6% of the females above 15 years. The corresponding figure in a normal population was 4.8 %. Among females with mild von Willebrand's disease a heavy loss of blood occurred generally in association with obstetric complications. One of the reasons why heavy bleeding at delivery was relatively uncommon was certainly that AHF and the bleeding time had approached normal values towards the end of pregnancy. When bleedings occurred they often did so about one week or more after parturition (Fig. 1). This was probably because after delivery the bleeding times and AHF-values relatively soon return to their original levels.

According to various authors, particularly Horowitz and O'Leary (1965), abortion is relatively common in women with von Willebrand's disease. We could not confirm this postulation in our series in which abortion occurred in 9 out of 86 women who had been pregnant.

Ovarian bleeding, which is not often reported in the literature, occurred in 9 of our female patients, including 8 with severe von Willebrand's disease. In addition, some women were operated upon because of ovarian cysts which might have formed as a result of follicular bleedings.

In contrast with what was seen in several other forms of bleeding, gastrointestinal haemorrhage was most common in adult age. The bleedings were often serious and in 6 of our cases of certain or probable von Willebrand's disease they were fatal. One patient has for several years been disabled by recurrent gastric haemorrhage. Only in a few cases had roentgen examination revealed ulcer or some other source of bleeding (Table 17).

Haematuria was uncommon and rarely serious. In three cases it was the symptom that brought the patient

to examination and led to the diagnosis of von Willebrand's disease.

Joint bleedings in von Willebrand's disease are uncommon but were nevertheless seen in about half of our patients with severe von Willebrand's disease. A search of the literature and personal observations showed that when joint bleedings occurred, it was nearly always in patients with very low AHF-values. In patients with AHF less than 10 % (most often 1.5–5.0 %) in our series movement was sometimes permanently impaired in some of the joints but the patients were not disabled. Roentgen examination then showed bone and joint changes of the type seen in haemophilia.

Tooth extraction often causes profuse bleeding in von Willebrand's disease and in at least two of our patients such extraction was followed by a considerable blood loss. Bleeding after tooth extraction was sometimes obstinate and recurred in several cases about one week after the operation.

According to the literature, postoperative haemorrhage has otherwise occurred particularly after otorhino-laryngological and stomatological operations (Imerslund 1949 and others, page 100). Severe bleeding has been reported after hysterectomy (Hill & Taylor 1968 and others, page 101, while other abdominal operations are said to carry only a relatively slight risk of bleeding (Eriksson 1962 and others, page 101).

In the Swedish series only a few operations have been performed without specific prophylactic treatment in patients with the severe type of von Willebrand's disease (Table 22). Major operations in those cases have been followed by severe bleeding, and in one case the loss of blood after operation on a bleeding ovarian cyst was fatal. Even minor operations, such as uterine curettage, have been followed by serious bleeding complications in patients with the severe form of the disease.

Also almost half of the operations on patients with the mild type of von Willebrand's disease were, however, accompanied or followed by remarkable bleeding (Table 23). Such postoperative bleeding was fatal in two cases of gastric resection. It was probably a main contributory cause of death in one case after thoracocentesis and in one after subtotal thyroidectomy. Life-threatening bleedings occurred after tonsillectomy and hysterectomy. Bleedings after division of the root of the trigeminal nerve because of neuralgia caused permanent neurological symptoms.

Bleeding after various operations have, as bleedings

after delivery and tooth extraction, often been obstinate with late exacerbations (Fig. 3, page 104).

Postoperative bleedings thus appear to constitute a severe problem in von Willebrand's disease. All operations on patients with the disease in the severe form and all major operations on patients with the disease in the mild form should therefore be given adequate prophylaxis. It is then also important that the operator is well aware of the patient's haemorrhagic disease so that he may pay special attention to haemostasis during the operation.

Bleeding in von Willebrand's disease is most common during childhood and adolescence (page 105), and decreases notably with increasing age. Exceptions are gastric bleeding and postoperative bleeding.

DIAGNOSIS

In the present investigation the diagnosis was based on a bleeding tendency associated with low AHF and prolonged bleeding time, at least according to Ivy. In the family studies the bleeding disease could, as a rule, be demonstrated also in some of the close relatives of the probands. In several cases platelet adhesiveness according to Salzman was found to be reduced. On administration of Fraction I-O or fresh plasma it was found that the AHF rose successively and that the bleeding time usually became shorter. The criteria for the diagnosis were more rigorous for the probands than for their relatives (see page 13).

The evaluation of the patient's history and the examination methods have several sources of error. In addition, the results of laboratory studies vary owing to such factors as physical exertion, mental stress, infection and pregnancy (see pages 108–110). We were also able to demonstrate a slow rise of the AHF with age (see page 109).

These sources of error create difficulties in the diagnosis, especially of the mildest cases with borderline values. In such cases some of the examination findings are not infrequently normal, while others argue for the presence of the disease in the mild form. In the investigations of relatives it was often difficult despite repeated examinations to decide whether a person had the disease or not. We then used the term "intermediate results". Genetic evaluation with regard to the probable frequency of the disease in parents and children of the probands suggested that in these cases we were dealing with persons predisposed to the disease but in

whom, owing to weak expressivity, the disease had not become manifest.

The relation between the bleeding tendency and the results of laboratory studies were judged with the aid of correlation tables (see page 111). The bleeding tendencies of the different patients were graded and related to mean values for AHF, bleeding time according to Duke and according to Ivy and platelet adhesiveness according to Salzman. The tables showed a closer correlation between the bleeding history and values for AHF and bleeding time than between history and values for platelet adhesiveness. But the bleeding time according to Duke was usually normal in patients with a mild predisposition to bleeding and often also in patients with moderate bleeding symptoms. On the other hand, in many cases the bleeding time according to Ivy rose to more than 30 minutes, even when the bleeding tendency was very mild.

The values obtained with the different examination methods were also related to one another (Tables 35–39). Statistical calculation with rank correlation (Table 40) showed a clear correlation between deviations from the normal concerning AHF and bleeding time. The correlation was less clear when platelet adhesiveness according to Salzman was correlated with other laboratory values.

The correlation found between AHF and bleeding time is of particular interest in the discussion of the inheritance in von Willebrand's disease (see page 84).

In the differential diagnosis of von Willebrand's disease the condition must be distinguished from mild haemophilia A, thrombasthenia and primary platelet dysfunction. In three families we encountered diagnostic difficulties in the distinction of von Willebrand's disease from these diseases. We established the diagnosis by administration of Fraction I—0 and following the AHF values and bleeding time for the next few days.

PROGNOSIS

Patients with severe von Willebrand's disease may have severe bleeding symptoms during childhood and adolescence. The symptoms, however, generally improve later and even in severe cases the prognosis is, broadly speaking, good, especially with the therapeutic possibilities now available.

Deaths from bleeding have been compiled partly from the literature and partly from the present material

(Table 43). The distribution of these cases among different bleeding symptoms is fairly similar in the two compilations. Gastric bleeding has been the commonest cause of death followed by intracranial bleeding and postoperative bleeding. Haemoptysis has formerly sometimes been the cause of death from haemorrhage, probably most often in cases of tuberculosis.

It is thus important that gastro-intestinal bleeding in patients with von Willebrand's disease be carefully treated. Head injuries and major operations require specific prophylaxis of bleeding, especially in severe von Willebrand's disease.

Considerably reduced working capacity has occurred mostly as a result of frequently recurrent gastric bleeding and menorrhagia. Joint bleeding has occasionally resulted in permanent impairment of range of movement of joints, but has not caused disability of the type seen in severe haemophilia.

Menorrhagia and heavy bleeding at delivery has sometimes made it necessary to perform hysterectomy or roentgen castration. Present therapeutic methods with hormone preparations can probably now make such operations unnecessary.

The risks of the child of a patient with von Willebrand's disease developing clinically manifest bleeding symptoms is, as judged from genetic studies in our material, about 40 %. The probability of severe bleeding symptoms is much smaller: barely 5%, and it appears to be less important whether the affected parents have the disease in the mild or severe form. If a parent has a severely ill child, the risks of later children also having severe bleeding symptoms is considerable. Thus, in three of our families two siblings have severe von Willebrand's disease but in only one family has one patient the severe form of the disease and a sibling the mild form.

THERAPY AND PROPHYLAXIS

The discovery of AHF-deficiency and deficiency of an inhibitor of bleeding in the plasma (the von Willebrand-factor) has made it possible since the middle of the 1950s to offer specific prophylaxis and therapy for bleedings in von Willebrand's disease.

At operations and tooth extractions, Fraction I-O and fresh plasma have been given prophylactically to Swedish patients with von Willebrand's disease (Tables

44, 45 and 46). With such prophylaxis it has been possible to perform major operations also upon patients with the severe form of the disease. Only in a few cases have serious bleeding complications occurred. The occurrence of an anticoagulant was suspected in one case. It has proved necessary to continue treatment for a sufficiently long time after the operation since postoperative bleeding of patients with von Willebrand's disease often occurs relatively late, *i.e.* after about a week or more. Treatment with fresh plasma alone has, as a rule, not been able to prevent postoperative bleeding after operations on patients with severe von Willebrand's disease and sometimes not after major operations on patients with the mild form of the disease.

In two cases delivery of patients with the severe form of the disease and with low AHF required extensive therapy to cope with the prolonged bleeding tendency from the vagina in the puerperium (Table 47).

Spontaneous bleeding, refractory to local measures has proved to respond favourably to Fraction I-O and fresh plasma (Table 48). The bleeding usually promptly ceased but sometimes required intense prolonged therapy, especially gastric bleeding.

The effect of Fraction I-O and fresh plasma on AHF, bleeding time and platelet adhesiveness, was studied. It proved possible to maintain AHF at desired level, except in two cases with signs of circulating anticoagulants. The bleeding time according to Duke could, as a rule, be promptly normalised, but only for a short time. With the doses used and given at intervals longer than 12 hours it was sometimes not possible to maintain a normal bleeding time in severely ill patients. Preparations of Fraction I-O manufactured in large batches from fresh frozen plasma have sometimes had a less satisfactory effect on the bleeding time. When the bleeding time was severely prolonged, bleeding often occurred despite high AHF-values. The bleeding time according to Ivy responded but little to the specific therapy. Platelet adhesiveness according to Salzman was not affected by the treatment.

As for side-effects, signs of anticoagulants have been observed in one patient, who had received treatment with Fraction I-O and fresh plasma. One patient developed moderately severe hepatitis after treatment with Fraction I-O. Otherwise no serious complications occurred.

The result of treatment with ϵ -ACA and AMCA is difficult to judge because, as a rule, the patients have received also some other treatment.

Corticosteroids have been tried in one case but without success.

In menorrhagia modern oral contraceptives have proved to have a favourable effect. In 4 cases where the laboratory values were followed it was, however, not possible to demonstrate any obvious effect on the AHF,

bleeding time or platelet adhesiveness (Table 50). The effect on menorrhagia therefore seems to be ascribable mainly to a local effect on the endometrium. The patients, however, felt that during treatment with "p-pills" they had reduced bleeding tendency also from other organs.

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ADDENDUM

In 1971—1972 important observations made at the Coagulation Laboratory, Malmö, have influenced our conception of von Willebrand's disease. These observations are briefly summarised in the following "Addendum" by Lars Holmberg.

GENETIC VARIATIONS OF VON WILLEBRAND'S DISEASE

by

Lars Holmberg

von Willebrand's disease is characterised by a low AHF-activity in the plasma and a prolonged bleeding time (Nilsson et al. 1957). These criteria together with reduced platelet adhesiveness, as measured according to Salzman (1963), have hitherto constituted the diagnostic criteria for von Willebrand's disease. Typical of the disease is also the response to infusion of factor VIII concentrate (Fraction I-O, cryoprecipitate). Infusion of such concentrates in patients with von Willebrand's disease normalises the bleeding time and often produces a retarded increase of the AHF activity in the plasma. This effect has been ascribed to the von Willebrand factor, *i.e.* a plasma factor lacking in von Willebrand's disease but occurring in normal plasma and in plasma in haemophilia A (Nilsson et al. 1959, Cornu et al. 1961).

Recent years have, however, witnessed the development of further possibilities of diagnosing von Willebrand's disease as well as an increase in our knowledge of the molecular nature of factor VIII in the plasma and the relation of this factor to the von Willebrand factor. The AHF activity is linked to a very high molecular weight plasma protein complex. This complex can be isolated, and the method generally used is gel chromatography in agarose (Hershgold et al. 1967, Johnson et al. 1967, Paulssen et al. 1969, Ratnoff et al. 1969, van Mourik & Mochtar 1970). Investigations using an immunologic technique have shown that patients with haemophilia A possess this protein complex, but in a biologically inactive form. Investigations by Stites et al. (1971) and Zimmerman et al. (1971) in a few patients with von Willebrand's disease suggested that these patients have little or no AHF related antigenic material in the plasma.

Some of the Swedish patients with von Willebrand's disease presented in this thesis have now been examined immunologically for AHF related antigen. The AHF activity was isolated from human Fraction I-O by agarose gel chromatography (chromatography in agarose gel) in a buffer system containing Rheomacrodex® according to van Mourik and Mochtar (1970). UV absorbing material appeared with the void volume and contained most of the AHF activity recovered. The fraction appeared homogenous. Thus fibrinogen, γ -globulin and α_2 -macroglobulin could not be demonstrated immunologically. Rabbits were immunised with this fraction and a monospecific antigen was prepared. This produced only one precipitation line with Fraction I-O and with plasma. Antiserum has anti-

AHF activity in an *in vitro* test system with plasma (Holmberg and Nilsson 1972).

The amount of AHF related antigenic material was determined by Laurell's method of electrophoresis in agarose gel containing antibodies. The electrophoresis was run in 0.075 M barbital buffer, pH 8.6, with 0.01 M EDTA. The analysis was carried out on plasma. If the plasma contains only little AHF related antigen the precipitation line tends to be less well defined, especially if the content is less than 10 to 15 % (of normal). The analysis was therefore performed also on cryoprecipitate of plasma from patients, and then it was possible to measure the lower concentrations. The agreement between the values found in plasma and in cryoprecipitate was good.

Twenty-three families from the Swedish series of von Willebrand's disease have so far been examined with the immunological method (Holmberg and Nilsson 1972). It was found that 51 patients belonging to 15 families had a low content of AHF related antigenic material. All affected members of these families had low values, while unaffected members had normal values. However, 19 patients belonging to 8 families had normal values of AHF related protein. All affected members of these 8 families showed the same pattern. Judging from these investigations, there appears to be a genetic variation in von Willebrand's disease. In type 1 of the disease the content of AHF related protein is always low. In type 2, on the other hand, it is normal, as in haemophilia. The families with type 1 and type 2, respectively, are given in Tables 1 and 2. The most severely affected patients with type 1 of the disease have also the lowest content of the AHF related protein. Patients with mild symptoms of the disease have only moderately reduced values.

In families belonging to type 1 the mode of inheritance is well compatible with autosomal dominant heredity. Examples of transmission of the condition from the father to the son are families 5, 6, 14, 17, 42, 58.

In the 8 families with von Willebrand's disease of type 2, *i.e.* with a normal content of AHF related protein, none of the affected males had had affected sons, and of the members studied, none of the affected men studied had healthy daughters. Examples are families 55 and 100. The mode of inheritance in these families are obviously X-chromosomal. As a rule, the male members had symptoms more often than the females, in whom the disease was discovered in family studies of members who had often had no symptoms. They were thus sometimes only carriers of the disease.

It would thus appear as if von Willebrand's disease, which has hitherto been regarded as a single clinical entity with a unique molecular pathology is in reality 2 separate diseases. Type 1 corresponds to the classical type of von Willebrand's disease with prolonged Duke bleeding time in severe cases and, as a rule, with low platelet adhesiveness according to Salzman. Severe cases with prolonged Duke bleeding time also occur in type 2 but, as a rule, the Duke bleeding time is normal and only the Ivy bleeding time prolonged. Further, adhesiveness according to Salzman is often normal. It

appears that von Willebrand's disease, type 2, is a separate disease with a clinical picture closely resembling that of the classical type of von Willebrand's disease, but with certain features resembling those of mild haemophilia A, especially regarding its mode of inheritance. Occasional families with similar characteristics have been described previously (Egeberg 1965).

Further research of the molecular structure of factor VIII may help to reveal the relationship between the two diseases.

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Table 1
Families with von Willebrand's disease Type I

	AHF %					
	Activ.	Imm.	Ivy (min)	Duke (min)	Salzman %	Symptoms
Fam. 1						
EB	20	0		>30	10	Severe
BT	8	0		>30	7	Severe
Fam. 5						
PP	23	29	30	9	9	Mild
WP	28	38	21	16	6	Mild
Fam. 6						
AF	60	36	19	5	3	Mild
RF	6	7	>30	>30	10	Severe
Fam. 10						
MA	10	<1	>30	>30	0	Severe
Fam. 11						
GB	24	6	>30	>30	3	Severe
Fam. 12						
KPA	5	0	>30	>30	2	Severe
Fam. 14						
BJ	20	11	>30		0	Mild
GJ	19	8	>30	8	0	Mild
LJ	38	19	>30	6	0	Mild
RJ	39	8	>25	3	10	Mild
Fam. 17						
LL	41	20	>30	2	61	Mild
Fam. 23						
KW	26	5	>30	>30	13	Severe
Fam. 42						
HN	43	18	>30	8	0	Mild
AS	47	33	>30	2	0	Mild
IA	42	27	25	4	5	Mild
SP	29	27	>30	24	2	Mild
IN	48	25	30	2	35	Mild
AF	36	16	>30	5	7	Mild
KE	29	10	>30			Mild
NA	54	23			10	Mild
BA	38	30	28	4	1	Mild
KS	43	12		23	7	Mild
JIA	44	27	>30	2	6	Mild
LA	58	50	17	1	0	Mild
P	55	53	>30	5	39	Mild
JEF	48	17	15	2	31	Mild
JN	40	17			0	Mild
ME		11				Mild
HE	30	12		4		Mild
AA	37	27	>30	3	19	Mild
GA		28			4	Mild
PS	21	19	>25	8-15	34	Mild
BIS	53	23	>30	4	0	Mild

(continued)

	Activ.	AHF% Imm.	Ivy (min)	Duke (min)	Salzman%	Symptoms
Fam. 58						
KF	45	23	>30	8	11	Mild
IF	45	13	>30	7		Mild
AF	40	37	>30	5-30	0	Mild-Severe
Fam. 60						
IJ	35	15	>30	8		Mild
MB	48	17	23	2	18	Mild
MJ	63	25	30	6		Mild
LJ	30	7	>30	>30		Severe
AB	62	33	15	5	3	Mild
JB	33	21	21		14	Mild

Table 2
Families with von Willebrand's disease Type II

Fam. 28						
AS m	16	225	>30	>30		Severe
JBK f	38	110	19-9	4	15	Mild
LH m	47	112	>30	5	24	Mild
RH m	27	75	24	3	47	Mild
IN f	26	122	15-18	4	19	Mild
AK f	25	87	15	4	6	Mild
Fam. 55						
MBP f	59	120	12	3	0	Mild
LF f	52	122	12	3		Mild
GF m	32	144	>30	3		Mild
RF m	33	116	15	4	89	Mild
Fam. 100						
MS f	35	72	19	3	30	Mild
AS m	20	88	30		49	Severe
Fam. 107						
MB f	45	124	>30	7	11	Mild
CB f	77	91	>30	11		Mild

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